SPIRIVA® HANDIHALER®

(TIOTROPIUM BROMIDE INHALATION POWDER)

ACADEMY OF MANAGED CARE PHARMACY (AMCP)

FORMULARY DOSSIER

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)
ACADEMY OF MANAGED CARE PHARMACY DOSSIER

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Formulary Dossier - Section 2

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EXECUTIVE SUMMARY

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United States[1] and throughout the world.[2] In 2000, an estimated 10 million US adults reported physician-diagnosed COPD.[1] An additional 14 million adults have evidence of impaired lung function but have not been diagnosed.[1] Data from the NHANES III estimated the true prevalence of the disease to be much higher, with approximately 24 million U.S. adults having evidence of lung function impairment.[1]

The prevalence of COPD increases with age.[3] However, contrary to common perceptions, data from the National Health Interview Survey indicate that approximately 70% of COPD patients are less than 65 years of age.[1] Furthermore, in a recent study of managed care enrollees, approximately one half of patients with COPD seeking health care services were in the 45 to 64 year-old age group.[4] According to the Global Burden of Disease Assessment, in 1990, COPD was ranked 12th in terms of global economic burden of disease, and by 2020, it is expected to be ranked 5th.[5] In the United States, total economic costs associated with COPD exceeded $37 billion in 2004.[3] The majority of direct costs (i.e., health expenditures) associated with COPD are a consequence of hospitalizations, which are related to acute exacerbations of the disease.[3,6] Further, dyspnea, the subjective sensation of shortness of breath, is a major symptom of COPD and worsens as the disease progresses. Dyspnea leads to substantial reductions in patients' functional capacity (e.g., walking), ability to perform activities of daily living, and health-related quality of life (HRQoL).[7]

Several classes of pharmacologic agents are available for maintenance treatment of COPD. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines and the American Thoracic Society/ European Respiratory Society (ATS/ERS) Standards for the Diagnosis and Management of Patients with COPD[8], regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Long-acting bronchodilators now include two classes of medication, long-acting beta-adrenergic agonists and long-acting anticholinergic, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder), considered by major guidelines to be a first-line maintenance medication for COPD. Bronchodilators are central to the management of COPD and current guidelines recommend a stepwise approach to treatment. That is, maximizing the dose and frequency of one bronchodilator before adding a second. A second bronchodilator may be added and doses adjusted based on the assessment of disease severity. Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with no increase in side effects.[9]

Although bronchodilators have been demonstrated to improve COPD symptoms, they are often underused. Results of a recent retrospective managed care claims analysis of 23,596 COPD patients showed that only 58.1% of patients received a bronchodilator. Less than one third (32%) of the COPD population received inhaled anticholinergics and less than one half (48%) received inhaled beta$_2$-agonist therapy.[10]

Another challenge in the management of patients with COPD is improving patient adherence to prescribed medication regimens. Multiplicity of medications and frequent dosing make it difficult for patients to adhere to treatment.[11] Poor compliance is common in patients with COPD and may have a negative effect on patient outcomes.[11,12]

SPIRIVA® HandiHaler® (SPIRIVA) is the first once-daily inhaled bronchodilator indicated for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.[13] SPIRIVA consistently provides sustained improvements in lung function for at least 24 hours.

The recommended dosage is 1 capsule (18 µg) once daily, administered via the HandiHaler® inhalation device. The HandiHaler® was specifically designed for use with the SPIRIVA capsule.[13]

SPIRIVA addresses many of the challenges of maintenance therapy for patients with COPD, offering physicians a new option for providing superior bronchodilation with once-daily dosing.[13]

In pivotal clinical trials, consisting of four 1-year and two 6-month clinical trials, SPIRIVA provided significant improvement in lung function, as well as significant reduction in dyspnea compared to placebo and ipratropium.[14-16] SPIRIVA significantly reduced exacerbations compared to placebo and ipratropium.[14-16] SPIRIVA reduced hospitalizations due to exacerbations compared to placebo.[14,15] Thus, SPIRIVA reduced health care resource use in addition to improving clinical outcomes.

It is important to note that all patients in the aforementioned clinical trials, including the placebo groups were provided with rescue albuterol and were allowed to continue theophylline compounds, oral or inhaled corticosteroids, and mucolytics, but not long-acting beta$_2$-agonists (LABAs) and inhaled anticholinergics. In effect, all patients including those randomized to placebo, were permitted to use all classes of airway medications, with the exception of inhaled anticholinergics, in an open label fashion, consistent with previously prescribed usual care. All patients in the one-year ipratropium controlled trials received an anticholinergic agent during the treatment period, randomly assigned to blinded treatment with either tiotropium or ipratropium.

In clinical trials, SPIRIVA demonstrated the following key outcomes:

Lung function

- Significant improvement in peak and average* $FEV_{1,}$ and FVC compared to placebo ($p<0.01$)[14] and ipratropium ($p<0.05$)[15]

  **Average FEV_1 and FVC over time were estimated by analysis of area under the curve (AUC) over the observation period and standardized for time.*

Exacerbations/hospitalizations

- Significantly fewer exacerbations compared to placebo (20% reduction, $p=0.045$) and ipratropium, (24% reduction, $p=0.006$)[15]

- Significantly fewer COPD-related hospitalizations compared to placebo, (41% reduction, $p<0.05$)[14]

- Significantly fewer exacerbations compared to placebo in a 6 month VA trial (5.7% reduction, $p=0.037$)[17]

Improvement in exercise endurance

- Significant increases in exercise endurance during constant work rate cycle ergometry compared to placebo in two randomized, double-blind, placebo-controlled trials ($p<0.05$)[18,19]
- Significant increases in exercise endurance during constant speed treadmill exercise combining SPIRIVA with pulmonary rehabilitation alone $p<0.05$)[20]

Dyspnea

- Significant reduction in dyspnea as measured by the Transition Dyspnea Index (TDI) focal score compared to placebo ($p<0.001$)[14] and ipratropium ($p<0.05$)[15]

Health-related quality of life (HRQoL)

- Significant improvement in HRQoL as measured by the St. George's Respiratory Questionnaire (SGRQ) total score compared to placebo ($p<0.05$)[14] and ipratropium ($p=0.001$)[15]

- Significant improvement in SGRQ total score at all time points, compared to placebo ($p<0.01$)[16]

Reduction in concomitant medications

- Significant reduction in rescue bronchodilator use compared to ipratropium ($p<0.05$)[15] and placebo ($p<0.01$)[14]

- Significantly fewer patients required oral steroids for exacerbations compared to placebo ($p<0.01$)[21]

In the 6-month clinical trials, SPIRIVA resulted in a significant improvement in lung function, TDI focal score, SGRQ total score and number of exacerbations relative to placebo. In addition, SPIRIVA significantly improved peak and average FEV_1 and FVC compared to salmeterol ($p<0.05$).[16,22] The latter finding has been substantiated by a recently completed 12 week comparison trial.[23]

In four 1-year and two 6-month clinical trials enrolling 2,663 patients with COPD, 1,308 of whom were treated with SPIRIVA, the agent was well tolerated. The most commonly reported adverse drug reaction was dry mouth, which was usually mild and often resolved during continued treatment.[13] SPIRIVA has been coadministered with other agents commonly used for the treatment of COPD (i.e., sympathomimetic bronchodilators, methylxanthines, and oral and inhaled corticosteroids), but its use with other anticholinergic-containing agents as maintenance therapy has not been studied and is therefore not recommended.[13]

Prospective cost-effectiveness analyses conducted alongside these pivotal clinical trials found that improvements in health outcomes were associated with reductions in health resource utilization (primarily hospital admissions and hospitalization days). In addition, a pharmacoeconomic model was developed to adapt the clinical trial results to the US setting for the purpose of estimating the cost-effectiveness and total budget impact of SPIRIVA in the maintenance treatment of COPD. Based on the model results in the US setting, patients treated with SPIRIVA have fewer severe and nonsevere exacerbations and lower mean resource use per year compared with patients receiving ipratropium, salmeterol, and Advair 250/50. The base case cost-effectiveness analysis demonstrated that SPIRIVA is more effective and less costly (*i.e.,* dominant) compared with ipratropium, salmeterol, and Advair 250/50. The cost-effectiveness of SPIRIVA occurs without consideration of the potential socioeconomic benefits from improvements in dypnea and health-related quality of life.

Sensitivity analyses validated that the model was robust to changes in key variables, with the main cost driver being hospitalization costs. The incremental pharmacy budget expenditure associated with the use of SPIRIVA for maintenance treatment of COPD is offset by decreased utilization of other health care resources, resulting in a net total budget savings.

Overall, clinical trials have demonstrated the long-term efficacy and safety of SPIRIVA in maintenance treatment of COPD, including chronic bronchitis and emphysema. Use of SPIRIVA resulted in notable improvements in lung function, dyspnea, and HRQoL. Additionally, treatment with SPIRIVA was associated with a reduction in COPD

exacerbations and related healthcare utilization, including hospitalizations.[14-16] The once-daily dosing of SPIRIVA may lead to improved patient compliance. Pharmacoeconomic analyses comparing SPIRIVA to ipratropium, salmeterol, and Advair 250/50 have demonstrated that use of SPIRIVA in the maintenance treatment of COPD is cost effective and results in a net savings in total budget.

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SPIRIVA® HANDIHALER® PRODUCT INFORMATION

4.1 SPIRIVA® HANDIHALER® PRODUCT DESCRIPTION

SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder) is a once-daily, inhaled bronchodilator indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1]

Generic Name	tiotropium bromide inhalation powder
Brand Name	SPIRIVA HandiHaler
Therapeutic Class	anticholinergic bronchodilator
American Hospital Formulary Service (AHFS) Drug Classification	12:08.08: antimuscarinics/antispasmodics

Each SPIRIVA capsule contains 18µg tiotropium (equivalent to 22.5µg tiotropium bromide monohydrate) blended with lactose monohydrate (5mg) as the carrier. Patients with a documented allergy to lactose should not use SPIRIVA (see **Contraindications**). Capsules are light green, with TI 01 printed on one side and the Boehringer Ingelheim company logo on the other side.[1]

SPIRIVA packaging will allow for a 30-day supply. Six SPIRIVA capsules are packaged in an aluminum/PVC/ aluminum blister card. Like all dry powders for inhalation, SPIRIVA is moisture sensitive. Therefore, care must be taken to preserve the integrity of the packaging. One blister card consists of two blister strips each containg 3 capsules and joined along a perforated-cut line. The blister cavity should only be opened and the capsule removed immediately before use.[1] The blister strip should be carefully opened to expose one capsule at a time.[2] After using the first capsule, the two remaining capsules should be used over the next 2 consecutive days. SPIRIVA capsules should always be stored in the blister. [1]

SPIRIVA should be stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).[1]

4.2 SPIRIVA AVAILABILITY[1]

Dosage Form	Strength	Package Size	NDC Code	AWP ($)	WAC ($)
Capsules	18µg	6 SPIRIVA capsules (1 blister card) and 1 HandiHaler	0597-0075-06	32.52	26.00
Capsules	18µg	30 SPIRIVA capsules (5 blister cards) and 1 HandiHaler	0597-0075-37	120.00	96.00

4.3 DOSAGE AND ADMINISTRATION

The recommended dosage of SPIRIVA is 1 capsule (18 µg) once-daily, using the HandiHaler® inhalation device.[1,3-6]

SPIRIVA capsules are for inhalation only and must not be swallowed.[1]

No dosage adjustment is required for geriatric, hepatically impaired, or renally impaired patients.[1] However, as with other agents that are predominantly excreted renally, advanced age is associated with decreased renal clearance of SPIRIVA, which may be explained by age-related reductions in renal function. Therefore, patients with moderate to severe renal impairment (CrCl of $\leq$ 50mL/min) given SPIRIVA should be monitored closely.[1]

4.4 HANDIHALER® INHALATION DEVICE

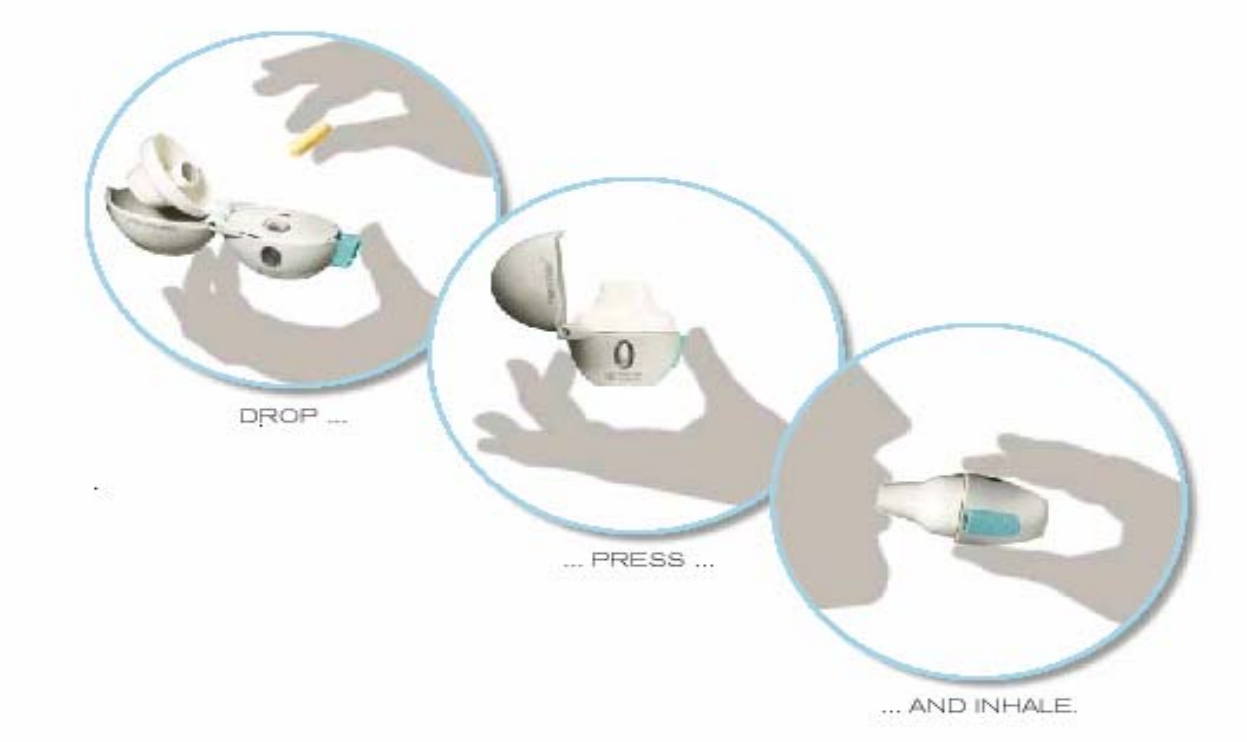
a. Description and Key Features of the HandiHaler

The HandiHaler is a reusable inhalation device used to administer the dry powder contained in the SPIRIVA capsule. The dry powder can be inhaled from the HandiHaler at flow rates as low as 20L/min. Under standardized *in vitro* testing, the HandiHaler delivers a mean of 10.4µg tiotropium when tested at a flow rate of 39L/min for 6.2 seconds. In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) with varying degrees of lung function compromise [mean FEV1 1.02L; 37.6% of predicted, the median peak inspiratory flow (PIF) through the HandiHaler was 30.0L/min (range 20.4 to 45.6L/min). Thus, the HandiHaler is a breath-actuated device that can effectively deliver medication to COPD patients.[1]

b. How to Use the HandiHaler

To administer SPIRIVA, the dust cap and mouthpiece are opened, a capsule is placed in the central chamber of the HandiHaler and the mouthpiece is closed firmly (until a click is heard), leaving the dust cap open. The capsule is pierced by pressing and releasing the button on the side of the inhalation device.[1,2] The patient then inhales through the

mouthpiece dispersing the tiotropium formulation into the air stream.[1] A single SPIRIVA capsule is administered once-daily using this method.[1]



c. Utility Across a Range of Disease Severity

To deliver enough medication to the lungs via a breath-actuated dry powder device, a patient with COPD must be able to generate a sufficient inspiratory flow rate (IFR).[3] This is important for patients of all disease severities from milder to more severe disease.[4]

The HandiHaler is an effective delivery device that can be used even by patients with substantially reduced airflow. In vitro studies have shown that the SPIRIVA powder is evacuated at IFRs as low as 20 L/min.[3]

Since delivery of the powder is dependent on a person's IFR, Chodosh and colleagues studied 26 patients with COPD across a wide range of disease severity (the percent of predicted FEV_1 ranged from 15% to 65%).[3] All patients achieved sufficient inspiratory flow to deliver medication using the HandiHaler.[3] (see Table 4.1).

Table 4.1: Peak Inspiratory Flow Rates (L/min) Observed With the HandiHaler[3]

Percent Predicted FEV_1	No. of Patients	Minimum (L/min)	Maximum (L/min)	Median (L/min)
46%-65%	8	28.2	45.0	32.7
28%-45%	10	21.6	45.6	30.3
≤27%	8	20.4	35.4	26.7
All patients	**26**	**20.4**	**45.6**	**30.0**

d. Ease of Use

Dahl and colleagues evaluated patients' ability to correctly use the HandiHaler compared to a metered dose inhaler (MDI) four weeks after receiving brief instructions and a demonstration.[5] Study results revealed that patients could easily learn how to use the HandiHaler, with significantly fewer errors in performance compared with those who were taught how to use an MDI. Patient performance with the HandiHaler was better than that with an MDI, even in those with prior MDI experience.[5]

4.5 SPIRIVA PHARMACOLOGY

a. Mechanism of Action

SPIRIVA is a long-acting, specific antimuscarinic agent, that is often referred to as an anticholinergic.[1] The long duration of action (24 hours) of SPIRIVA allows for once-daily dosing.[1] SPIRIVA has similar affinity to all 5 muscarinic receptor subtypes (M_1 to M_5).[1] Of these muscarinic subtypes, only M_1-, M_2-, and M_3-receptors have been identified in human airways.[6]

- **M_1-receptors**: facilitate ganglionic transmission and enhance cholinergic reflex effects in the airways
- **M_2-receptors**: have an autoinhibitory effect on acetylcholine release
- **M_3-receptors**: mediate the bronchoconstrictor and mucus secretory responses to acetylcholine and cholinergic nerve stimulation

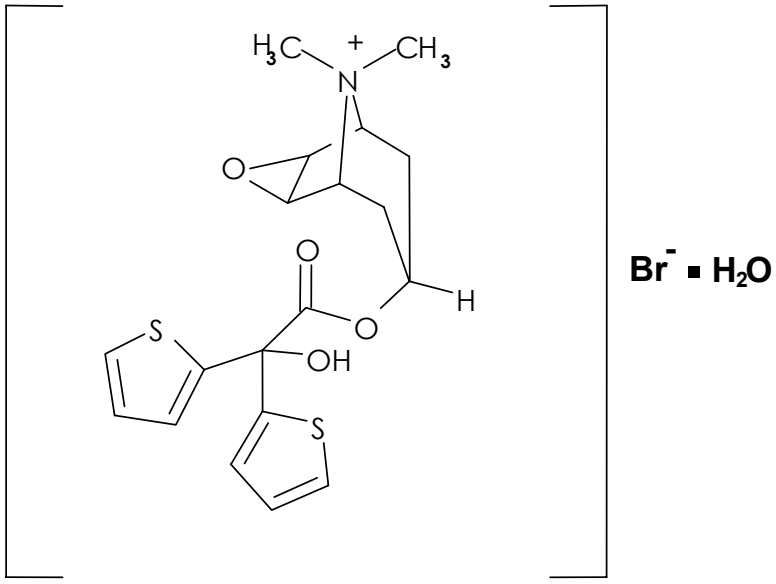
In the airways, SPIRIVA exhibits pharmacologic effects through prolonged inhibition of M_3-receptors at the smooth muscle, leading to bronchodilation.[1] The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations.[1]

In preclinical *in vitro* and *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours.[1]

SPIRIVA is an N-quaternary anticholinergic administered by inhalation. The resulting bronchodilation is predominantly site-specific[1], not systemic. Dissociation from M_3-receptors is slower than from M_1-receptors. Dissociation from M_1-receptors is slower than from M_2-receptors. The slow dissociation from M_3-receptors may explain the clinical findings of significant and long-acting bronchodilation in patients with COPD[1] allowing for once-daily dosing for SPIRIVA.[7]

b. Description/Chemistry

Tiotropium bromide monohydrate is an anticholinergic with specificity for muscarinic receptors.[1] It is a synthetic, nonchiral, quaternary ammonium compound.[1]



Animal models have demonstrated that the chemistry of SPIRIVA (positively charged N-quaternary structure), is responsible for the lack of gastrointestinal (GI) absorption and limits transport across the blood-brain barrier, minimizing systemic side effects.[8]

c. Pharmacologic Market Comparison

A comparison of the pharmacologic properties of SPIRIVA and other agents used in COPD can be found in Table 4.2.

Table 4.2: Pharmacologic Comparison of Key Agents Used in COPD

	SPIRIVA®	Combivent®*		Advair 250/50®[13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent®)[9]***	**albuterol sulfate (multiple brands)[10]***	**salmeterol xinafoate (Serevent® Diskus)[11]†**	**fluticasone propionate (Flovent® Diskus) [12]**
Indication	COPD	COPD	Reversible obstructive airway disease	Asthma COPD	Asthma
		For Combivent: COPD only		**For Advair 250/50**: Asthma and for COPD with chronic bronchitis (in COPD reevaluate after 6 months of therapy)	
Dosing Schedule	Once daily	Four times per day	Four to six times per day	Twice daily	Twice daily
Type of Formulation	Dry powder inhaler	Metered dose inhaler	Metered dose inhaler	Dry powder inhaler	Dry powder inhaler
Chemical Entity	Synthetic, nonchiral, quaternary ammonium compound	Synthetic quaternary ammonium compound, chemically related to atropine	Short-acting, relatively selective $beta_2$-adrenergic receptor agonist	Long-acting, highly selective $beta_2$-adrenergic receptor agonist	Synthetic trifluorinated glucocorticoid
Molecular Weight	490.4	430.4	239.3	603.8	500.6
Therapeutic Category	Anticholinergic	Anticholinergic	$Beta_2$-adrenergic agonist	$Beta_2$-adrenergic agonist	Corticosteroid
Mechanism of Action	Binding of acetylcholine to M_3 receptors triggers events that lead to bronchoconstriction, an enzyme called guanyl cyclase is activated. Guanyl cyclase converts a chemical called guanosine triphosphate (GTP) to another chemical, cyclic guanosine monophosphate (cGMP). In bronchial smooth muscle tissue, cGMP	Binding of acetylcholine to M_3 receptors triggers events that lead to bronchoconstriction, an enzyme called guanyl cyclase is activated. Guanyl cyclase converts a chemical called guanosine triphosphate (GTP) to another chemical, cyclic guanosine monophosphate (cGMP). In bronchial smooth muscle tissue, cGMP	$Beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle. Cyclic adenosine monophosphate (AMP), formed from adenosine triphosphate (ATP) in $beta_2$-adrenergic cells, mediates cellular	$Beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle. Cyclic adenosine monophosphate (AMP), formed from adenosine triphosphate (ATP) in $beta_2$-adrenergic cells,	The precise mechanism of action of fluticasone propionate is not known. It is known that it acts as a potent anti-inflammatory in human lung tissue. Corticosteroids have been shown to inhibit multiple cell types (ie.,

	SPIRIVA®	Combivent®*		Advair 250/50®[13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent®)[9]***	**albuterol sulfate (multiple brands)[10]***	**salmeterol xinafoate (Serevent® Diskus)[11]†**	**fluticasone propionate (Flovent® Diskus)[12]**
	stimulates calcium to flow into the muscle cells (influx) which causes bronchial smooth muscles to contract and airways constrict. Acetylcholine binding to M_3 receptors stimulates goblet cells and the submucosal glands to produce mucus. Anticholinergic agents compete with acetylcholine for muscarinic receptor binding sites—when an anticholinergic agent binds to a receptor, acetylcholine cannot bind to the receptor and its normal actions are blocked That is, acetylcholine is unable to stimulate bronchoconstriction or mucus production.[14,15] The dissociation half-life from the M_3 receptor for tiotropium is 34.7 hours.[7]	stimulates calcium to flow into the muscle cells (influx) which causes bronchial smooth muscles to contract and airways constrict. Acetylcholine binding to M_3 receptors stimulates goblet cells and the submucosal glands to produce mucus. Anticholinergic agents compete with acetylcholine for muscarinic receptor binding sites—when an anticholinergic agent binds to a receptor, acetylcholine cannot bind to the receptor and its normal actions are blocked That is, acetylcholine is unable to stimulate bronchoconstriction or mucus production.[14,15] The dissociation half-life from the M_3 receptor for ipratropium is 0.26 hours.[7]	responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells	mediates cellular responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.	mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils).

*Combivent® is a combination of ipratropium bromide and albuterol sulfate.
**Advair Diskus® is a combination of salmeterol xinafoate and fluticasone propionate
†The xinafoate moiety has no apparent pharmacologic activity.
Atrovent and Combivent are registered trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.
Serevent, Flovent and Advair are registered trademarks of GlaxoSmithKline.

4.6 SPIRIVA PHARMACOKINETIC PROFILE

Table 4.3 compares the pharmacokinetic profiles of SPIRIVA with those of ipratropium, albuterol, salmeterol and fluticasone.

Table 4.3: Pharmacokinetic Comparison of Key Agents Used in COPD

	SPIRIVA®	Combivent®*		Advair 250/50®13**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1, 14,15]	**ipratropium bromide (Atrovent)[9,16,14,15*]**	**albuterol sulfate (multiple brands)[10,16*]**	**salmeterol xinafoate (Serevent Diskus)[11]**	**fluticasone propionate (Flovent Diskus) [12]**
Onset of Action	30 minutes	15 minutes	5 minutes	30-48 minutes	24 hours
Duration of Action	24 hours	3-6 hours	3-4 hours	12 hours	12 hours
Peak Action	3 hours	1-2 hours	1-1.5 hours	3-4 hours	~ 48 hours
Absorption	19.5% Suggests that fraction reaching the lung is highly bioavailable. Maximum SPIRIVA plasma concentrations observed 5 minutes after inhalation	Atrovent is not readily absorbed into the systemic circulation either from the surface of the lung or from the GI tract, as confirmed by blood levels and renal excretion studies	Gradual	Low or undetectable systemic levels	18%
Volume of Distribution	32 L/kg	4.6 L/kg	9.1 L/kg	Not reported	4.2L/kg
Plasma Protein Binding	72%	Not reported	Not reported	96%	91%
Steady State	14-21 days Peak plasma concentrations: 17-19 pg/mL	Not reported	Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation at recommended	Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic (xinafoate) moieties are	Fluticasone acts locally on the lung tissue; therefore plasma levels do not predict therapeutic effect.

	SPIRIVA®	Combivent®*		Advair 250/50®[13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1, 14,15]	**ipratropium bromide (Atrovent)[9,16,14,15*]**	**albuterol sulfate (multiple brands)[10,16*]**	**salmeterol xinafoate (Serevent Diskus)[11]**	**fluticasone propionate (Flovent Diskus) [12]**
	Trough plasma concentrations: 3-4 pg/mL Local concentrations not known		doses. Administration of titrated albuterol by inhalation to 4 subjects resulted in maximum plasma concentrations within 2 to 4 hours. However, data from urinary excretion studies indicated that albuterol has an elimination half-life of 3.8 hours	absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect	
Elimination Half-life	5-6 days	~2 hours	3.8 hours	5.5 hours The inactive xinafoate moiety has a long elimination half-life of 11 days	~7.8 hours
Metabolism	Extent of biotransformation is small Cytochrome P450 (CYP) 2D6 and 3A4 are responsible for elimination of small part of dose	Partial	Not reported	Extensive hydroxylation in the liver	17β-carboxylic acid is a circulating metabolite having negligible pharmacologic activity which is a derivative of fluticasone propionate formed through the cytochrome P450 3A4 pathway.

	SPIRIVA®	Combivent®*		Advair 250/50®[13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1, 14,15]	**ipratropium bromide (Atrovent)[9,16,14,15*]**	**albuterol sulfate (multiple brands)[10,16*]**	**salmeterol xinafoate (Serevent Diskus)[11]**	**fluticasone propionate (Flovent Diskus) [12]**
Elimination	14% of an inhaled dose is eliminated via urinary excretion. The remainder is eliminated via feces as nonabsorbed drug Pharmacokinetic steady state reached after 2-3 weeks, with no accumulation thereafter	50% excreted unchanged in urine in 24 hours	Approximately 72% of the inhaled dose is excreted in the urine within 24 hours, 28% as unchanged drug and 44% as metabolite	25% urine, 60% feces	Following oral dosing, less than 5% was excreted in the urine as metabolites, the remainder excreted in the feces as parent drug and metabolites
Elderly	Advanced age may be associated with decreased tiotropium renal clearance	Not reported	Not reported	The pharmacokinetics of salmeterol base have not been studied in elderly patients	Pharmacokinetic studies have not been carried out in elderly patients
Hepatic Impairment	The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics	Not reported	Not reported	Because salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to salmeterol accumulation in plasma. Therefore, patients with hepatic disease should be closely monitored	Because fluticasone is predominantly cleared by the liver, impairment of liver function may lead to accumulation in the plasma. Therefore, patients with hepatic disease should be closely monitored.

	SPIRIVA®	Combivent®*		Advair 250/50®13**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1, 14,15]	**ipratropium bromide (Atrovent)[9,16,14,15*]**	**albuterol sulfate (multiple brands)[10,16*]**	**salmeterol xinafoate (Serevent Diskus)[11]**	**fluticasone propionate (Flovent Diskus) [12]**
Renal Impairment	Renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both IV infusion and dry powder inhalations Mild renal impairment (creatinine clearance [CrCl] 50-80 mL/min) was associated with a 39% increase in area under the curve $(AUC)_{0-4}$ after IV infusion In patients with COPD and CrCl <50 mL/min, IV administration was associated with an 82% increase in AUC_{0-4}	Not reported	Not reported	The pharmacokinetics of salmeterol base have not been studied in elderly patients or in patients with hepatic or renal impairment	The pharmacokinetics of fluticasone propionate have not been studied in patients with renal impairment

*Combivent® is a combination of ipratropium bromide and albuterol sulfate.
**Advair Diskus® is a combination of salmeterol xinafoate and fluticasone propionate
†The xinafoate moiety has no apparent pharmacologic activity.
Atrovent and Combivent are registered trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.
Serevent, Flovent and Advair are registered trademarks of GlaxoSmithKline.

4.7 SPIRIVA SAFETY INFORMATION

a. Contraindications

SPIRIVA is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, i.e., ipratropium, or to any component of this product.[1]

b. Warnings

SPIRIVA is intended as a once-daily maintenance treatment for patients with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., as rescue therapy).[1] Immediate hypersensitivity reactions, including angioedema, may occur following administration of this agent.[1]

c. Precautions

General

- As an anticholinergic agent, SPIRIVA may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and should be used with caution in patients with any of these conditions[1]
- Inhaled medicines may cause inhalation-induced bronchospasm[1]
- As a predominantly renally excreted drug, patients with moderate to severe renal impairment (CrCl $\leq$50mL/min) treated with SPIRIVA should be monitored closely[1] for the potential of increased anticholinergic side effects from the increased plasma concentrations of tiotropium.

Drug/Drug Interactions

Although no formal drug interaction studies have been performed, SPIRIVA has been administered concomitantly with other agents commonly used in patients with COPD, without adverse reactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled corticosteroids. The coadministration of SPIRIVA with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.[1]

Drug/Laboratory Test Interactions

None are known.[1]

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in rats, and there was no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes in vitro.[1]

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of ≥0.078 mg/kg/day (approximately 35 times the recommended human daily dose [RHDD] on a mg/m^2 basis).[1] No such effects were observed at 0.009 mg/kg/day (approximately 4 times the RHDD on a mg/m^2 basis).[1] The fertility index, however, was not affected at inhalation doses of ≤1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m^2 basis).[1]

Pregnancy

Pregnancy Category C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of ≤1.471 and 0.007 mg/kg/day, respectively.[1] These doses correspond to approximately 660 and 6 times the RHDD on a mg/m^2 basis in the respective species.[1] However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pups' sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg/day (approximately 35 times the RHDD on a mg/m^2 basis).[1] In rabbits, an increase in postimplantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m^2 basis).[1] Such effects were not observed at inhalation doses of 0.009 and ≤0.088 mg/kg/day in rats and rabbits, respectively.[1] These doses correspond to approximately 4 and 80 times the RHDD on a mg/m^2 basis, respectively.[1] These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.[1]

There are no adequate, well-controlled studies in pregnant women. SPIRIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

Use in Labor and Delivery

The safety and effectiveness of SPIRIVA have not been studied during labor and delivery.[1]

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. Although it is not known

whether tiotropium is excreted in human breast milk, caution should be exercised if the agent is administered to a nursing woman.[1]

Pediatric Use

The safety and effectiveness of SPIRIVA in pediatric patients have not been established.[1]

Geriatric Use

Of the total number of patients who received SPIRIVA in the 1-year clinical trials, 426 were <65 years of age, 375 were 65 to 74 years of age, and 105 were ≥75 years of age. Within each age-group, there were no differences between the proportion of patients with adverse events in the SPIRIVA and comparator groups for most events.[1] Dry mouth increased with age in the SPIRIVA group (differences from placebo were 9.0%, 17.1%, and 16.2% in to the aforementioned age-groups, respectively).[1] A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA group in placebo-controlled studies.[1] The differences from placebo for constipation were 0%, 1.8%, and 7.8%, respectively, for each of the age-groups.[1] The differences from placebo for urinary tract infections were –0.6%, 4.6%, and 4.5%, respectively, for each of the age-groups.[1] No overall differences in effectiveness were observed among these age groups. Based on available data, no adjustment of SPIRIVA dosage in geriatric patients is warranted.[1]

d. Adverse Reactions

Of the 2,663 patients who were enrolled in controlled clinical trials (including four 1-year and two 6-month, randomized, double-blind studies), 1,308 were treated with SPIRIVA at the recommended dose of 18μg once daily.[1] The most commonly reported adverse drug reaction was dry mouth, which was usually mild and often resolved during continued treatment.[1] Other reactions reported in individual patients, consistent with possible anticholinergic effects, included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.[1]

Adverse Events in Long-Term Studies

The adverse events observed in long-term clinical trials are listed in Table 4.4 and include all events, whether considered drug-related or non-drug-related by the investigator.[1]

Four multicenter, 1-year, controlled studies evaluated SPIRIVA in patients with COPD.[1] Table 4.4 shows adverse events that occurred with a frequency of ≥3% in the SPIRIVA group and that exceeded placebo by ≥1% in the 1-year placebo-controlled trials. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.[1] In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age.(see **Precautions, *Geriatric Use***)

Two multicenter, 6-month, studies compared SPIRIVA to salmeterol and placebo in patients with COPD.[1] The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.[1]

Table 4.4: Adverse Event Incidence (% of patients) in 1-Year COPD Clinical Trials[1]

Body System (event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n=550)	Placebo (n=371)	SPIRIVA (n=356)	Ipratropium (n=179)
Body as a Whole				
Accidents	13	11	5	8
Chest pain (nonspecific)	7	5	5	2
Edema, dependent	5	4	3	5
GI System Disorders				
Abdominal pain	5	3	6	6
Constipation	4	2	1	1
Dry mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	3
Sinusitis	11	9	3	2
Upper respiratory tract infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary tract infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA treatment group, but were <1% in excess of the placebo group.[1]

Other events that occurred in the SPIRIVA group at a frequency of 1% to 3% in the placebo-controlled trials and in which the rates exceeded those in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *GI System Disorders:* GI disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic*

and Nutritional Disorders: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Resistance Mechanism Disorders:* herpes zoster; *Respiratory System Disorder (upper):* laryngitis; *Vision Disorder:* cataract.

In addition, among the adverse events observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia[17], angioedema, and urinary retention. [1]

The following adverse reactions have been identified during worldwide post-approval use of SPIRIVA: dizziness, epistaxis, hoarseness, palpitations, pruritus, tachycardia, throat irritation, and urticaria.[1]

e. Safety Attributes of Key Agents Used in COPD

See Table 4.5 for safety attributes of key agents use in COPD.

Table 4.5: Safety Attributes of Key Agents Used in COPD

	SPIRIVA®	Combivent®*		Advair 250/50® 13**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent® Inhalation Aerosol)[9,18,19*]**	**albuterol sulfate (multiple brands)[10,20*]**	**salmeterol xinafoate (Serevent Diskus®)[11,21]**	**fluticasone propionate (Flovent Diskus)[12]**
Black Box Warning	None	None	None	**For Advair 250/50 and Serevent Products: WARNING:** Long-acting beta 2 agonists, such as salmeterol, one of the active ingredients in Advair Diskus, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe Advair Diskus for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo).	
Pregnancy Category	C	B	C	C	C
Carcinogenesis, Mutagenesis, Impairment of Fertility	No tumor/cancer No mutations No fertility problems	No tumor/cancer No mutations No fertility problems	Tumorigenicity shown for albuterol in some animal studies No tumor/cancer studies in humans No mutations No fertility problems	Tumorigenicity shown for salmeterol in some animal studies No tumor/cancer studies in humans No mutations No fertility problems	No tumorigenicity shown in animal studies No mutations No fertility problems
Use in Labor and Delivery	Safety not studied	Safety not studied	Beta-agonists may potentially interfere with uterine contractility	No well-controlled studies in humans. Beta-agonists may potentially interfere with uterine contractility	Safety not studied

	SPIRIVA®	Combivent®*		Advair 250/50® [13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent® Inhalation Aerosol)[9,18,19]***	**albuterol sulfate (multiple brands)[10,20]***	**salmeterol xinafoate (Serevent Diskus®)[11,21]**	**fluticasone propionate (Flovent Diskus)[12]**
Use in Nursing Mothers	Not known	Not known	Not known	Not known	Not known, but since other corticosteroids are distributed into milk, caution is advised
Pediatric Use	Safety and efficacy not established	Safety and efficacy not established	Safety and effectiveness in children <4 yrs of age have not been established	Safety and efficacy in pediatric patients <4 yrs of age have not been established	Studies have shown that inhaled corticosteroids cause a reduction in growth in pediatric patients. Children and adolescents receiving Flovent should be monitored routinely. Safety and efficacy in pediatric patients <4 yrs of age have not been established. In fixed comination with salmeterol (Advair Diskus) safety has not been established in patients <12 yrs old
Geriatric Use	No dose adjustment necessary./ Follow creatinine clearance in those individuals with moderate to severe renal impairment	Inhalation has been tested in patients ≥65 years of age and is not expected to cause side effects different from those experienced in younger populations	Dose selection should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and/or drug therapy	No dose adjustment necessary	No substantial differences in safety and efficacy relative to younger adults.
Adverse Drug Reactions	Dry mouth was usually mild and often resolved during continued treatment. Other reactions included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention	Dryness of mouth, cough, irritation from aerosol, headache, nausea, dizziness, blurred vision, tachycardia, glaucoma, urinary difficulty and retention, fatigue, insomnia, skin rash, angioedema of the tongue, lips, and face. Urticaria, laryngospasm, and anaphylactic reaction have been	Adverse reactions to albuterol are similar in nature to those with other $beta_2$-adrenergic agonists, i.e., tachycardia; palpitations; nervousness, tremor, sleeplessness; angina; hypertension; unusual taste;nausea; throat irritation; dizziness; heartburn;	Adverse reactions to salmeterol are similar in nature to those with other $beta_2$-adrenergic agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm; headache; tremor; nervousness; paradoxical	Upper respiratory irritation and infection, sinusitis, rhinitis, oral candidiasis, nausea, gastrointestinal pain and discomfort, cough, bronchitis, viral infection, headache, musculoskeletal pain and injury, glaucoma, increased intraocular

	SPIRIVA®	Combivent®*		Advair 250/50® [13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent® Inhalation Aerosol)[9,18,19]***	**albuterol sulfate (multiple brands)[10,20]***	**salmeterol xinafoate (Serevent Diskus®)[11,21]**	**fluticasone propionate (Flovent Diskus)[12]**
		reported, with positive rechallenge in some patients. Many of the patients had a history of allergies to other drugs and/or foods, including soybean	immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and arrhythmias	bronchospasm; throat irritation; and nausea	pressure, cataracts
Precautions	Anticholinergics may potentially worsen symptoms and signs associated with narrow angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and should be used with caution in patients with any of these. Inhaled medicines can cause inhalation-induced bronchospasm.	Anticholinergics may potentially worsen symptoms and signs associated with narrow angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and should be used with caution in patients with any of these. Inhaled medicines can cause inhalation-induced bronchospasm.	Sympathomimetics should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines.	No effect on the cardiovascular system is usually seen with recommended doses of inhaled salmeterol, but the side effects common to all sympathomimetic drugs (i.e., increased blood pressure, heart rate, excitement) may occur after salmeterol use and may require discontinuation of the drug.	Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.
				For Advair 250/50: No effect on the cardiovascular system is usually seen with recommended doses of Advair, but the side effects common to all sympathomimetic drugs may occur after use of salmeterol, a component of Advair and may require discontinuation of the drug. Long-term use of inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD) and this poses an additional risk to some already at risk COPD patients. Glaucoma, increased intraocular pressure, and cataracts have occurred in patients following the long-term use of fluticasone, a component of Advair; therefore, regular eye exams should be considered.	
Recommended Monitoring	Patients with moderate to severe renal impairment (CrCl ≤ 50mL/min) treated with SPIRIVA should be monitored closely for the potential of increased		Patients are advised that if a previously prescribed dose fails to provide the usual response, this may be a sign of destabilization of asthma and	Patients should be cautioned about the potential adverse effects of palpitations, chest pain, rapid heart rate, tremor, or nervousness	Monitor for systemic and local corticosteroid effects such as glaucoma, oral fungal infection, and developmental delay (when used in young

	SPIRIVA®	Combivent®*		Advair 250/50® [13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent® Inhalation Aerosol)[9,18,19]***	**albuterol sulfate (multiple brands)[10,20]***	**salmeterol xinafoate (Serevent Diskus®)[11,21]**	**fluticasone propionate (Flovent Diskus)[12]**
	anticholinergic side effects from increased serum concentrations of tiotropium		medical attention should be sought (i.e., patient is not to increase the dose or frequency without consulting with a physician).		patients). The patient should not increase the prescribed dosage, but contact their physician if symptoms worsen or do not improve.
				For Advair 250/50: Patients are advised to obtain a baseline bone mineral density test and periodic tests while on Advair. Patients are advised to consider regular eye exams to test for intraocular pressure changes, glaucoma or cataracts. Physicians are to re-evaluate therapy after 6 months of Advair 250/50 treatment.	
Drug/Drug Interactions	Coadministration with other anticholinergic-containing agents (e.g., ipratropium) has not been studied and is thus not recommended	Coadministration with other anticholinergic-containing agents has not been studied and is thus not recommended	Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic agents are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects. Administer with extreme caution to patients being treated with monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs), or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Beta-blockers inhibit the pulmonary effect of beta-agonists and may also produce severe bronchospasm in patients with	Administer with extreme caution in patients being treated with MAOIs or TCAs, or within 2 weeks of discontinuation of such agents, since the action of salmeterol on the vascular system may be potentiated by the use of these agents. Beta-blockers inhibit the pulmonary effect of beta-agonists and may also produce severe bronchospasm in patients with asthma or COPD. Thus, these patients should not normally be treated with beta-blockers (except under such circumstances as prophylaxis following MI, and then with extreme caution). The ECG changes and/or hypokalemia that may result from administration of nonpotassium-sparing diuretics can be acutely worsened by beta-agonists, especially when the recommended beta-agonist dose is exceeded. Thus, caution is advised	Care should be exercised when fluticasone propionate is coadministered with ketoconazole, ritonavir and other known cytochrome P450 3A4 inhibitors, as this is the route of metabolism of fluticasone propionate.

	SPIRIVA®	Combivent®*		Advair 250/50® [13]**	
	tiotropium bromide (SPIRIVA® HandiHaler®)[1]	**ipratropium bromide (Atrovent® Inhalation Aerosol)[9,18,19]***	**albuterol sulfate (multiple brands)[10,20]***	**salmeterol xinafoate (Serevent Diskus®)[11,21]**	**fluticasone propionate (Flovent Diskus)[12]**
			asthma. Thus, these patients should not normally be treated with beta-blockers (except under such circumstances as prophylaxis following myocardial infarction [MI], and then with extreme caution). The electrocardiogram (ECG) changes and/or hypokalemia that may result from administration of nonpotassium-sparing diuretics can be acutely worsened by beta-agonist use, especially when the recommended beta-agonist dose is exceeded. Patients who are currently receiving digoxin and albuterol should be carefully monitored as serum digoxin levels may decline.	in the coadministration of these 2 classes of agents	
Drug/Lab Test Interactions	Not known	Not known	Not known	Not known	Abnormal short cosyntropin tests with higher doses

*Combivent® is a combination of ipratropium bromide and albuterol sulfate.
**Advair Diskus® is a combination of salmeterol xinafoate and fluticasone propionate
†The xinafoate moiety has no apparent pharmacologic activity.
Atrovent and Combivent are registered trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.
Serevent, Flovent and Advair are registered trademarks of GlaxoSmithKline.

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SPIRIVA'S PLACE IN THERAPY

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United States[1] and throughout the world.[2] In 2002, an estimated 12 million US adults reported physician-diagnosed COPD.[3] An additional 14 million adults have evidence of impaired lung function but have not been diagnosed.[1] According to the Global Burden of Disease Assessment, in 1990, COPD was ranked 12th in terms of global economic burden of disease, and by 2020, it is expected to be ranked 5th.[4] The majority of direct costs (i.e., healthcare expenditures) associated with COPD are attributable to hospitalizations for acute exacerbations.[5,6] In addition, dyspnea (i.e., shortness of breath) that is associated with COPD has a significant effect on patients as manifested by impaired health-related quality of life (HRQoL), reduced capacity for functional activities (e.g., walking), and decreased ability to perform activities of daily living.[7]

Long-acting bronchodilator therapy for COPD is recommended by all the major guidelines including GOLD and ATS/ERS as first-line maintenance treatment to prevent and control daily symptoms and to reduce the number of exacerbations and hospitalizations.[2,8] SPIRIVA is a long-acting, once-daily, inhaled anticholinergic bronchodilator that exhibits its effects via prolonged M_3-receptor blockade.[9] It was developed specifically for the treatment of COPD.[9] In an extensive clinical trial program involving 3,316 patients, use of SPIRIVA resulted in superior peak bronchodilator efficacy compared to ipratropium, salmeterol and placebo.[10,11,12,13] Patients treated with SPIRIVA experienced significant improvements in HRQoL and reductions in dyspnea and the number of exacerbations compared to ipratropium and placebo.[10,11] In addition, patients treated with SPIRIVA demonstrated a significant reduction in hospitalizations compared to placebo.[10] Use of SPIRIVA as first-line maintenance therapy for patients with COPD offers the opportunity for superior bronchodilation and improved patient management together with convenient once-daily dosing. SPIRIVA has the ability to provide patients and health care providers with clinical efficacy and economic value.

5.1 REVIEW OF COPD

a. Definition of COPD

According to the ATS/ERS Standards for the diagnosis and treatment of patients with COPD, COPD is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.[8] Pathologically, COPD is characterized by a combination of small airway disease (i.e., obstructive bronchiolitis, or chronic bronchitis) and parenchymal destruction (i.e., emphysema).[2] The relative contribution of chronic bronchitis vs. emphysema is difficult to determine precisely and varies from patient to

patient.[2] Exacerbations, characterized by such COPD symptoms as worsening shortness of breath and cough with increasing amounts of viscous sputum, are common.

Currently, there is no known cure for COPD, only smoking cessation can prevent disease progression.[14,15] However, supportive treatment can relieve patients' symptoms, particularly dyspnea, and improve HRQoL.[15]

b. Epidemiology of COPD

COPD is a leading cause of morbidity, mortality, and disability in the United States.[1] It is evident that COPD is a major public health problem.[2] Whereas mortality associated with the major chronic diseases (i.e., coronary heart disease and stroke) is decreasing, the prevalence of and deaths from COPD continue to rise.[16,17] In addition, data from the third National Health and Nutrition Examination Survey (NHANES III) indicate that although COPD is increasing in prevalence, a significant proportion of patients with the disease remain undiagnosed.[1]

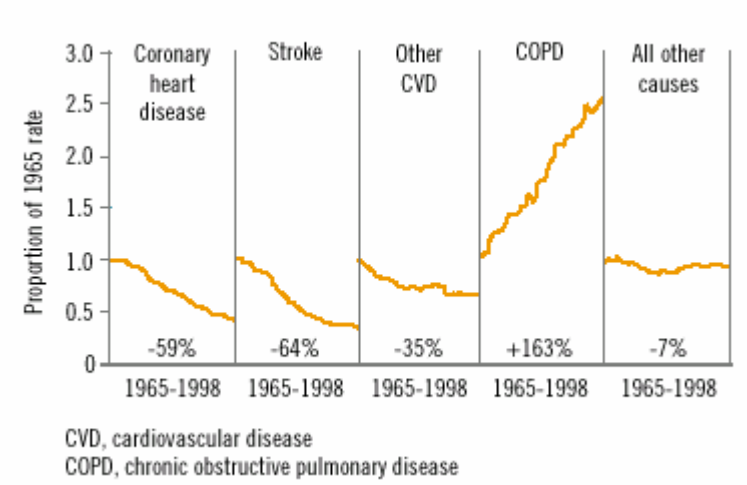
Prevalence

According to NHANES III, the prevalence of COPD in the US population is 6.8%, ranking it among the leading chronic illnesses in adults.[18] From 1982 to 1995, the number of individuals diagnosed with COPD increased by 41.5%. Each year, approximately 250,000 new cases of COPD are diagnosed.[19] During 2002, an estimated 12 million US adults reported physician-diagnosed COPD.[3] However, data from NHANES III estimated the true prevalence of the disease to be much higher, with approximately 24 million US adults having evidence of lung function impairment.[1] The prevalence of COPD increases with age.[5] However, contrary to common perceptions, data from the National Health Interview Survey indicate that approximately 70% of COPD patients are less than 65 years of age.[1] In a recent study of managed care enrollees, approximately one half of patients with COPD seeking health care services for their disorder were in the 45 to 64 year-old age group.[20] According to another managed care analysis conducted to assess the disease burden and patterns of COPD treatment, prevalence of the disorder tripled between 45 and 55 years of age—from 13.5 to 41.2 per 1,000 patients.[21] Another common misperception is that COPD predominantly occurs in the male population. However, data from the Centers for Disease Control indicate that women have had higher rates of self-reported COPD than men since 1980, and during 2000, the number of women who died from COPD surpassed the number for men.[1,8]

Morbidity and Mortality

In 2000, COPD was ranked as the fourth leading cause of death in the United States.[5] In contrast to mortality rates from the major cardiovascular diseases, which have been on the decline since the 1960s, deaths from COPD increased dramatically in the latter half of the 20th century (see Figure 5.1).[22]

Figure 5.1: Percent Change in Age-Adjusted Death Rates, United States, 1965-1998[22]



In 2000, COPD was responsible for an estimated 8 million ambulatory visits (28 visits per 1,000 population) to either physician offices or hospital outpatient departments[1,23] and 1.5 million emergency department visits (5 visits per 1,000 population).[1,23] COPD is a leading cause of hospitalization in US adults, particularly among the elderly.[1] Almost 726,000 hospitalizations (2.3% of total hospitalizations) were attributed to COPD in 2000.[1,2,4]

Dyspnea is the predominant symptom of COPD and can have a substantial adverse impact on patients' HRQoL, functional capacity, and the ability to perform activities of daily living.[7] Dyspnea, often described as a feeling of breathlessness, is the reason most patients seek medical attention.[2] It is a major cause of disability and anxiety associated with COPD.[2,25] Individuals with COPD also often experience dyspnea upon exertion, which leads to exercise intolerance.[2]

Exacerbations, defined as periods of worsening symptoms including increases in cough, sputum production and purulence, and dyspnea lasting for ≥2 days, are also a major cause of morbidity in patients with COPD.[26,27] Exacerbations are often associated with bacterial and viral infections of the airways and lungs,[28]and are a common cause of COPD-related hospitalizations.[29,30] The frequency and severity of exacerbations increase as the disease progresses.[31] Compared with the general population, persons with COPD have approximately twice as many hospitalizations, restricted activity days, and days confined to bed.[32]

c. Economic Burden of COPD

In 2004, the annual cost for COPD in the United States was approximately $37.2 billion, which includes health care expenditures (direct costs) of $20.9 billion and indirect costs of $16.3 billion.[5] Although the total annual cost for COPD in 2004 was lower than that

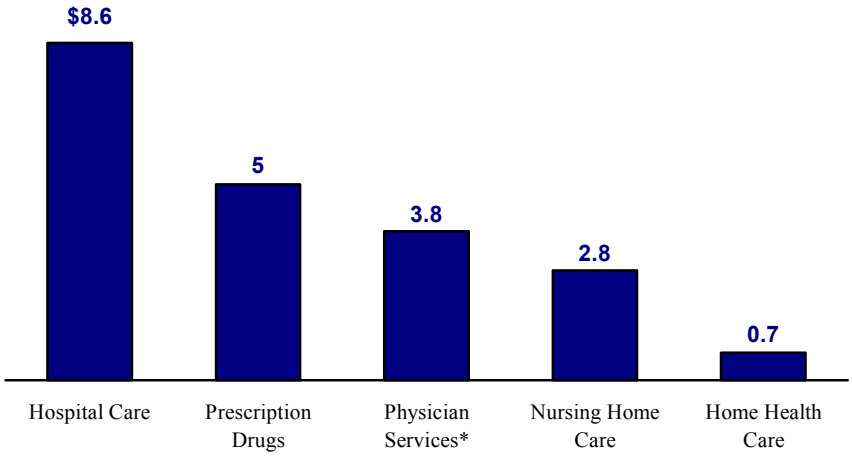
for stroke ($53.6 billion) and hypertension ($55.5 billion), it was more than twice the cost of asthma ($16.1 billion).[5]

Direct Costs of COPD

For a commercial insurer, health care resource utilization among patients with COPD is at least double that of members of the same sex and age without the disease.[20,33] Within managed care, studies have demonstrated that the average patient with health care claims in the United States has total health care charges of $179 per month. By contrast, the average total health care charge for patients with COPD is calculated at $1,109 per month.[20] In a study designed to estimate the costs of medical care for patients with COPD vs. those without the disease, respiratory-related per-person total annual health care costs for patients with COPD were 25 times those of matched controls, with the greatest portion of these costs attributed to inpatient hospitalizations. In patients with COPD, total annual respiratory costs were highest for those less than 65 years of age ($8,412).[34]

Over the last decade, the estimated annual number of hospitalizations attributed to COPD has risen every year, from 463,000 in 1990 to 726,000 in 2000.[1] Among the direct costs (i.e., health care expenditures) for COPD in 2004, hospital care was ranked the highest. Of $20.9 billion for total direct costs related to COPD, $8.6 billion was for hospital care [5] (See Figure 5.2).[5]

Figure 5.2: 2004 Direct Cost of COPD (billions of dollars)[5]



*Includes physicians, clinics, and other professional services.

Strassels and colleagues evaluated the medical resource use and costs incurred by individuals with COPD in the United States in 1987. Approximately 68% of direct medical costs in persons with COPD were attributed to inpatient hospitalizations.[35]

Within a managed care database representing 23,596 lives[36], 58% of COPD health care expenditures are for inpatient hospitalizations.[37] Thus, interventions that reduce or prevent hospitalizations in patients with COPD are likely to provide pharmacoeconomic value and have a major impact on the cost of treating the disease.[38]

Indirect Costs of COPD

COPD is associated with significant indirect costs. COPD can interfere with a person's ability to work, thus leading to on-the-job productivity losses, lost wages for workers, and lost revenue for employers.[39] Based on data from NHANES III, it is estimated that in 1994 COPD was responsible for lost productivity at work of approximately $9.9 billion.[40] In a recent study of 6 large employers (374,799 employees), COPD ranked sixth in terms of cost burden, ahead of osteoarthritis and breast cancer.[39]

d. Pathophysiology of COPD

Airflow limitation is the primary physiologic manifestation of COPD. The airflow limitation is the functional consequence of 3 major processes: airway smooth muscle constriction, inflammation and remodeling of the airways and destruction of lung parenchyma. The smooth muscle constriction is mediated primarily by cholinergic tone.[41-43] Airflow limitation in COPD has both a reversible and irreversible component. Cholinergic tone is the major reversible component of airway obstruction in patients with COPD. In the lungs, acetylcholine released by postganglionic nerve endings stimulates airway smooth muscle contraction.[43] Vagal cholinergic tone refers to the basal activity of the autonomic nervous system, which is anatomically localized in the vagus nerve.[43] Cholinergic tone is present in both the COPD and the normal airway.[43] However, cholinergic tone has an increased impact in COPD where airflow is already compromised due to airway remodeling, muscle hypertrophy, increased mucous production, and destruction of surrounding parenchyma.[42,44] Thus, anticholinergic agents are particularly useful as bronchodilators for the treatment of patients with COPD.[42]

Muscarinic Receptors in the Human Airway

Three types of cholinergic receptors (muscarinic M_1, M_2, and M_3) are responsible for mediation of bronchoconstriction and have been identified in the human airway and lung.[45] Stimulation of M_3 receptors on airway smooth muscle by acetylcholine results in bronchoconstriction. The excitatory M_1-receptors are responsible for reflex bronchoconstriction. M_2-receptors have an inhibitory effect on acetylcholine release.[44] The ideal pharmacologic treatment for COPD, would preferentially block the M_1- and M_3-receptors, with no effect on the M_2-receptor.[45] SPIRIVA's binding affinity is similar for all three receptors, but its dissociation from M_3 is much slower than from M_1 which is much slower than from M_2.[46]

e. Clinical Presentation and Risk Factors for COPD

Cigarette smoking is the predominant risk factor for COPD.[8,47] Although >80% of patients with COPD have a smoking history,[48] not all smokers develop COPD. The often quoted statistic that only 15% of smokers actually develop COPD may under represent the prevalence of the disease. A recent study suggests that at as many as 50% of smokers develop evidence of obstructive lung disease.[8,14] Currently, it is not possible to identify smokers who are likely to develop COPD.

Patients with COPD are typically 40 years of age or older, have a history of cigarette smoking, and have progressive symptoms of cough and dyspnea on exertion.[49,50] Although chronic cough, with or without sputum production, is usually the first symptom of COPD to develop, dyspnea is the hallmark disease symptom and is usually the primary reason that patients seek medical attention.[2]

Mild and moderate COPD often remain undiagnosed. These patients may adapt their lifestyles to lessen discomfort and do not seek medical attention until their symptoms become more severe.[51,52] By the time patients present to the health care system, they often have significant impairment in lung function, which might have been prevented with smoking cessation. As COPD progresses, symptoms of dyspnea worsen[53] and exacerbation frequency increases,[31,53,7] with patients developing progressive exercise intolerance and ultimately the need to curtail activities of daily living.[6] Although COPD is progressive in nature, when appropriately maintained on bronchodilators, lung function can be improved, exacerbations can be reduced, and patients may experience improvements in dyspnea and HRQoL.[6,54,55]

Differential Diagnosis: COPD vs. Asthma

Distinguishing COPD from asthma, especially in smokers, can be challenging.[16,56] As the underlying pathophysiology of asthma and COPD differs, distinguishing between the two diseases in order to optimize therapeutic interventions is important. For example, although both diseases have an inflammatory component, asthma is characterized primarily by eosinophilic inflammation, and patients with asthma thus respond well to inhaled corticosteroids (ICS). Stable COPD, on the other hand, involves mainly neutrophilic inflammation, which is poorly responsive to ICS.[55-57] Table 5.3 compares the characteristics of each disease.[59,60]

Table 5.1: Differential Diagnosis of COPD vs. Asthma[1,2,58,59,60]

	COPD	ASTHMA
Age of onset	Usually > 40 years	Any age (usually in childhood)
Smoking history	Usually >10 pack-years	Unrelated
Symptom pattern	Usually chronic, slowly progressive	Varies day to day
Airway reversibility	Partially reversible	Largely reversible
Steroid response in stable disease	Minimal (≈15%)	Present

f. Current Treatment Patterns

The goals of pharmacologic therapy include preventing and controlling symptoms of COPD, reducing the frequency and severity of exacerbations, increasing exercise tolerance, and improving patients' HRQoL.[2] Decreasing exacerbations through pharmacologic treatment reduces health care costs[61] and improves patients' HRQoL.[27,62] COPD exacerbations requiring hospitalization are associated with substantial risk of mortality both during the hospitalization and in the subsequent year; therefore, reducing admissions to the hospital for COPD should be a goal of therapy.

Management of Stable COPD

The overall approach to the management of patients with stable COPD is characterized by a stepwise increase in treatment modalities, based on the severity of the disease.[2]

Nonpharmacologic Treatment

Smoking cessation is the single most clinically effective and cost-effective way to reduce the risk for COPD and to stop disease progression.[2,63,64] In addition, exercise training and pulmonary rehabilitation programs have been shown to benefit patients with COPD.[65]

Pharmacotherapy

Bronchodilators are central to the management of stable COPD.[2,66] Short-acting $beta_2$-agonists are initially used on an as-needed basis. As COPD progresses, bronchodilators must be used on a regular basis as part of a maintenance regimen. Long-acting bronchodilators are the treatment of choice for the maintenance treatment of COPD, with anticholinergics often considered first-line maintenance therapy.[2,66,67] Current guidelines recommend a stepwise approach to treatment, maximizing the dose and frequency of one bronchodilator before adding a second.[2,67,69] A second bronchodilator may be added and doses adjusted based on disease severity. Since many patients with COPD use multiple inhaled medications, compliance is especially challenging.[68] Lack of adherence to

medication regimens is common among patients with COPD and may have a negative effect on patient outcomes.[70] In recognition of the fact that regular treatment with long-acting bronchodilators is more effective and more convenient than short-acting bronchodilators, the 2004 Update to the GOLD Guidelines has recommended long-acting over short-acting bronchodilators for maintenance therapy.[2] The ATS/ERS guidelines note that SPIRIVA improves health status and reduces exacerbations and hospitalizations compared to placebo and ipratropium and appears to be superior to salmeterol in some measures during 6 months studies.[8]

Table 5.2: Effect of commonly used medications on important clinical outcomes[8]

	FEV_1	Lung volume	Dyspnea	HRQoL	AE	Exercise endurance	Mortality	Side effects
Short acting β -agonists	Yes (A)	Yes (B)	Yes (A)	NA	NA	Yes (B)	NA	Some
Ipratropium bromide	Yes (A)	Yes (B)	Yes (A)	No(B)	Yes (B)	Yes (B)	NA	Some
Long-acting β -agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	NA	Minimal
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	NA	Some
Theophylline	Yes (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (B)	NA	Important

FEV1: forced expiratory volume in one second; HRQoL: health-related quality of life; AE: exacerbation of COPD; NA: evidence not available.
GOLD grade levels are indicated in brackets Grade A: randomized clinical trial (RCT), rich body of data; Grade B: RCT, limited body of data.

Although inhaled corticosteroids are indicated for the maintenance treatment of asthma, data on their efficacy in COPD has been conflicting and hence the use of inhaled corticosteroids in the management of COPD remains somewhat ill-defined. According to the 2004 GOLD guidelines, "The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with a forced expiratory volume in 1 second [FEV_1] <50% predicted (Stage III: Severe COPD and Stage IV: Very Severe COPD) and repeated exacerbations."[2] The ATS/ERS guidelines contain similar recommendations for the use of inhaled corticosteroids in stable COPD.[8] There are no single agent inhaled corticosteroid formulations with FDA approval for the treatment of COPD in the United States. Advair 250/50, the fixed combination of the inhaled corticosteroid, fluticasone (250mg) and the LABA, salmeterol (50mcg), recently received FDA approval for use in patients with COPD associated with chronic bronchitis. Advair 500/50, which includes a higher dose

of the inhaled steroid, is not recommended or FDA approved for use in COPD as no additional improvement in lung function was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects. The benefit of treatment of patients with COPD associated with chronic bronchitis with Advair 250/50 for periods longer than 6 months has not been evaluated. Baseline and periodic follow up bone densitometry and ophthalmologic examinations are recommended due to the high risk of osteoporosis, glaucoma, increased intraocular pressure and cataracts in the COPD population and the potential association between the long-term administration of inhaled corticosteroids and the development of these conditions.[71]

5.2 ROLE OF SPIRIVA IN COPD

a. Role of SPIRIVA in Therapy

SPIRIVA is a once-daily, inhaled anticholinergic bronchodilator that has been shown to provide clinical benefits as maintenance therapy for patients with COPD, including those with chronic bronchitis and emphysema.[9] SPIRIVA can be combined with agents from other bronchodilator classes, further enhancing its bronchodilation effects.[72,73]

b. Expected Outcomes of SPIRIVA Therapy

SPIRIVA is the first once-daily, inhaled maintenance bronchodilator therapy for patients with COPD. In order to be most applicable to the setting of usual care, the controlled clinical trials with SPIRIVA permitted the use of concomitant theophyllines, inhaled steroids and modest doses of oral steroids as previously prescribed. In addition, all patients were provided with albuterol to use as needed. In these trials, SPIRIVA provided significant improvement in lung function compared with ipratropium, salmeterol and placebo, as well as significant reduction in dyspnea compared to placebo and ipratropium.[10,11,12,13,74]

Additionally, in an exercise tolerance study, reductions in hyperinflation and exertional dyspnea were accompanied by increased exercise endurance time.[74] Exercise endurance time was superior with SPIRIVA compared to placebo on days 21 ($p<0.05$) and 42 of treatment ($p<0.01$).[74] Moreover, SPIRIVA treated patients had improved inspiratory capacity compared to placebo treated patients during exercise, indicating decreased lung hyperinflation ($p<0.001$).[74,75] These findings indicate that SPIRIVA treated patients have a greater capacity to increase ventilation (i.e., breathing) during activity. A recently completed second clinical trial has confirmed this finding.[76]

In addition to improving clinical outcomes, SPIRIVA has been shown to reduce health care resource use.[12] SPIRIVA significantly reduced exacerbations compared to placebo and ipratropium[10-12,77] and COPD-related hospitalizations compared to placebo.[10,77] There was a trend toward lower resource use among patients receiving SPIRIVA compared to patients using salmeterol.[78]

SPIRIVA has a favorable safety and tolerability profile. The most common adverse drug reaction reported was dry mouth, which was mild and often resolved during continued treatment. The safety profile of SPIRIVA is similar to that of ipratropium bromide.[9] Given the evidence of improved patient outcomes and economic benefits, combined with superior bronchodilator efficacy and once-daily dosing, SPIRIVA is uniquely positioned as first-line maintenance therapy for patients with COPD.

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CLINICAL OUTCOMES FOR SPIRIVA®

6.1 SUMMARY OF STUDIES

The SPIRIVA clinical program included six pivotal phase III comparator trials. In additional to these trials, a 24-hour spirometry study was conducted to better characterize optimal timing of medication administration. A robust phase IIIB/IV clinical trial program was designed to further elucidate the efficacy of SPIRIVA and included a trial designed to prospectively evaluate the effect of SPIRIVA on the frequency of exacerbations of COPD and associated hospitalizations. An additional salmeterol comparison trial and two exercise tolerance studies were also conducted. These trials are summarized in Table 6.1 and will be described in detail in this section of the dossier.

The six pivotal phase III trials included a pair of one-year placebo controlled trials, a pair of one-year ipratropium controlled trials and a pair of 6-month placebo-controlled, salmeterol comparison trials. During the conduct of these trials all patients were permitted to continue using their usual respiratory medications for COPD, with the exception of anticholinergic agents and long-acting beta-agonist medications. In effect, all patients including those randomized to placebo, were permitted to use all classes of airway medications, with the exception of inhaled anticholinergics. All patients in the one-year ipratropium controlled trials received an anticholinergic agent during the treatment period, randomly assigned to blinded treatment of either SPIRIVA or ipratropium. A total of 2,663 patients with chronic obstructive pulmonary disease (COPD) were randomized into these pivotal clinical trials, 1,308 of whom were treated with SPIRIVA.[1]

Table 6.1: SPIRIVA Clinical Outcome Studies[1-14]

Trial	No. of Patients	Design
Phase III Comparator* Trials		
1-YEAR TRIALS		
SPIRIVA vs. placebo[1-4]	470	Multicenter randomized , double-blind, placebo-controlled
SPIRIVA vs. placebo[1-4]	451	Multicenter, randomized double-blind, placebo-controlled
SPIRIVA vs. ipratropium[1,3-5]	288	Multicenter, randomized, double-blind, double-dummy, ipratropium-controlled
SPIRIVA vs. ipratropium[1,3-5]	247	Multicenter, randomized, double-blind, double-dummy, ipratropium-controlled
6-MONTH TRIALS		
SPIRIVA vs. salmeterol vs. placebo[1,3,6,7]	623	Multicenter, randomized, double-blind, double-dummy, placebo- and salmeterol-controlled
SPIRIVA vs. salmeterol vs. placebo [1,3,6,7]	583	Multicenter, randomized double-blind, double-dummy, placebo- and salmeterol-controlled
Other Trials		
SPIRIVA and exacerbations and hospitalizations** [10]	1,829	Multicenter, randomized , double-blind, placebo-controlled, parallel group
SPIRIVA vs. salmeterol [9] Daytime lung function	653	Multicenter, randomized , double-blind, Double-dummy, salmeterol-controlled
SPIRIVA and exercise tolerance[12]	198	Multicenter, randomized double-blind, placebo -controlled
SPIRIVA and exercise tolerance[13,14]	261	Multicenter, randomized double-blind, placebo-controlled, parallel group
SPIRIVA in AM vs. PM dosing, 24-h spirometry trial [3,8]	121	Multicenter, randomized double-blind, placebo-controlled
Improvement in resting IC and hyperinflation in COPD patients with increased static lung volumes[11]	81	Multicenter, randomized, double-blind, , placebo-controlled

* Patients were permitted to continue using usual respiratory medications (i.e., rescue albuterol, theophyllines, oral and inhaled steroids, antibiotics, and mucolytics), with the exception of long-acting beta$_2$-agonists (LABAs) and anticholinergics. All patients in the one-year ipratropium controlled trials received an anticholinergic agent during the treatment period, randomly assigned to blinded treatment of either SPIRIVA or ipratropium.

** Long-acting beta$_2$-agonists (LABAs) were permitted in addition to all other usual respiratory medications (i.e., rescue albuterol, theophylline, oral and inhaled steroids, antibiotics, and mucolytics) with the exception of anticholinergics in this study group.

In the 1-year pivotal phase III trials, treatment with SPIRIVA resulted in the following clinical and patient-centered outcomes:

- Significant improvement in lung function compared to ipratropium and placebo.[2,5,6]
- Significant reduction in frequency of exacerbations compared to ipratropium and placebo [2,5,6]
- Significant reduction in COPD-related hospitalizations compared to placebo[2,5,6]
- Significant reduction in dyspnea compared to ipratropium placebo [2,5,6]

- Significant improvement in health-related quality of life (HRQoL) compared to ipratropium and placebo [2,5,6]

- Significant reduction in use of a rescue bronchodilator compared to ipratropium and placebo[2,3,5]

- Significant reduction in percentage of patients using oral steroids with SPIRIVA compared to placebo[3]

In the 6-month clinical trials, SPIRIVA resulted in a significant improvement in lung function, TDI focal score, SGRQ total score and number of exacerbations relative to placebo. In addition, SPIRIVA significantly improved peak and average FEV_1 and FVC compared to salmeterol ($p<0.05$).[6,7] The latter finding has been substantiated by a recently completed 12 week comparison trial.[9]

SPIRIVA was well tolerated in these trials, as described in Section 4 of this dossier.

6.2 STUDY DESIGNS AND OUTCOMES FOR PIVOTAL PHASE III TRIALS

The 6 pivotal SPIRIVA clinical trials shared similar study designs to provide consistency and allow comparisons across the trials. The studies included:

- Two 1-year trials comparing SPIRIVA to placebo

- Two 1-year trials comparing SPIRIVA to ipratropium

- Two 6-month trials comparing SPIRIVA to salmeterol and placebo

The placebo-controlled trials were conducted in 50 centers in the United States. The trials comparing SPIRIVA with ipratropium were conducted in 29 centers in Belgium and the Netherlands. One of the salmeterol studies was conducted in 39 centers in 12 countries (United States [5], Canada, Denmark, Germany, Italy, the Netherlands, Australia, Belgium, New Zealand, South Africa, Spain, United Kingdom). The other salmeterol study was conducted in 50 centers in 15 countries (United States [4], Australia, Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, South Africa, Sweden, United Kingdom).

Identical study designs were used to enable the pooling of data from each of the two pairs of 1-year trials. Similarly, data from two salmeterol and placebo controlled trials have been pooled for all outcomes except lung function over 12 hours.

Study Design/Objective

The pivotal SPIRIVA clinical trials were randomized, double-blind, parallel-group studies. Double dummy technique was used for the ipratropium and salmeterol comparison trials. Again, it should be emphasized that treatment groups, including

placebo groups were permitted to use maintenance theophyllines, inhaled steroids, modest doses of oral steroids as well as being provided with albuterol to use as needed. The trials were conducted to assess the long-term efficacy and safety of SPIRIVA 18 µg dry powder inhaled once daily via the HandiHaler® device in patients with COPD.[3]

Table 6.2: Inclusion and Exclusion Criteria Used in 6 Phase III Trials [2,3,5,6,15-17]

	SPIRIVA 18 µg qd vs. placebo, 1-year trial	**SPIRIVA 18 µg qd vs. ipratropium 40 µg qid, 1-year trial**	**SPIRIVA 18 µg qd vs. salmeterol 50 µg bid vs. placebo, 6-month trial**
Inclusion			
All patients had a diagnosis of COPD and met the following spirometric criteria:			
FEV_1	≤65% of predicted normal*; ≤70% of FVC	≤65% of predicted normal*; ≤70% of FVC	≤60% of predicted normal† ≤70% of FVC
Age	≥40 years	≥ 40 years	≥40 years
Smoking	≥10 pack-years	≥10 pack-years	≥10 pack-years
Exclusion			
Medical history	Asthma, allergic rhinitis, atopy, pulmonary resection, cancer, recent MI, hospitalization for heart failure, cardiac arrhythmia	Asthma, allergic rhinitis, atopy, pulmonary resection, cancer, recent MI, hospitalization for heart failure, cardiac arrhythmia	Asthma, allergic rhinitis, atopy, pulmonary resection, cancer, recent MI, hospitalization for heart failure, cardiac arrhythmia
Eosinophilia	≥600 cells/mm^3	≥400 cells/mm^3 (males); >320 cells/mm^3 (females)	≥600 cells/mm^3
Supplemental O_2	Regular use	Regular use	Regular use
Steroids	Prednisone >10 mg/day or the equivalent	Prednisone >10 mg/day or the equivalent	Prednisone >10 mg/day or the equivalent
Respiratory infection	Infection within preceding 6 weeks	Infection within preceding 6 weeks	Infection within preceding 6 weeks

* FEV_1 percent of predicted normal calculated by Morris equation
† FEV_1 percent of predicted normal calculated by ECCS (European Committee for Coal and Steel) equation
FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Enrollment Criteria and Patient Demographics

The major inclusion and exclusion criteria for the pivotal trials are shown in Table 6.2. These critieria were designed to include patients with stable COPD and to exclude those with asthma and potentially unstable, serious comorbid conditions.

All patients who participated in these trials were at least 40 years of age (range 43% to 55% under the age of 65 across all studies), and had a diagnosis of COPD with a smoking history of at least 10 pack-years. For the studies comparing SPIRIVA to placebo or

ipratropium, spirometric criteria were FEV_1 ≤65% of predicted normal and ≤70% of forced vital capacity (FVC). For the studies comparing SPIRIVA with salmeterol and placebo, spirometric criteria were FEV_1 ≤60% of predicted value and ≤70% of FVC.

Tables 6.2 and 6.3 also provide regimens received by each parallel group. During the treatment period, all patients who participated in the pivotal studies, including those randomized to placebo, were permitted to take their previously prescribed respiratory medications for COPD with the exception of long-acting beta-adrenegic agonsists (LABAs) and inhaled anticholingeric agents (other than study drug in the ipratropium controlled trials).[15-17] The respiratory medications permitted during the conduct of the trials included:

- Albuterol, as needed
- Theophylline compounds
- Inhaled corticosteroids
- Corticosteroids at the equivalent of up to 10 mg of prednisone/day and short term increases in steroid doses for the treatment of exacerbations
- Adjunctive agents
    - Antibiotics
    - Mucolytics (not containing bronchodilators)

Long-acting $beta_2$-agonists (LABAs) and anticholinergics apart from study medications were excluded.[2,5,15]

Table 6.3: Patient Demographics in 6 Phase III Trials[2-7]

	SPIRIVA vs. placebo, 1–year trial		**SPIRIVA vs. ipratropium, 1-year trial**		**SPIRIVA vs. salmeterol vs. placebo, 6-month trial**		
	SPIRIVA 18 µg qd	Placebo	SPIRIVA 18 µg qd	Ipratropium 40 µg qid	SPIRIVA 18 µg qd	Salmeterol 50 µg bid	Placebo
Randomized (n)*	550	371	356	179	402	405	400
Age (years, mean)	65.1	65.4	63.6	64.5	63.8	64.1	64.6
% less than Age 65 years	44	43	51	49	50	48	47
Gender (%)							
Male	67	63	84.3	86	77	75	76
Female	33	37	15.7	14	23	25	24
Mean Baseline FEV_1 (L)	1.04	1.00	1.25	1.18	1.12	1.07	1.09
Mean FEV_1 % predicted	39.1	38.1	41.9	39.4	39.2	37.7	38.7
FEV_1/FVC (%)	45.8	45.5	45.7	45.5	43.7	42.2	42.3

* Note use of 3:2 randomization for treatment groups in 1-year trials.
FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

Assessments

Major assessment parameters included[2-7]:

- Lung function testing—FEV_1 and FVC were assessed by spirometry; peak expiratory flow rate (PEFR) was measured at home, twice daily by peak flow monitor

- Dyspnea evaluation —Mahler Dyspnea Index: Baseline Dyspnea Index (BDI) and the Transition Dyspnea Index (TDI)

- Exacerbations of COPD and related hospitalizations – Exacerbations were defined by the presence of at least 2 new or increased respiratory symptoms (such as cough, dyspnea, sputum, wheeze) lasting at least 3 days and reported by the investigator as an adverse event

- HRQoL—St. George's Respiratory Questionnaire (SGRQ)

Details on assessment methods and flowcharts of assessment schedules are provided in Appendix 1.

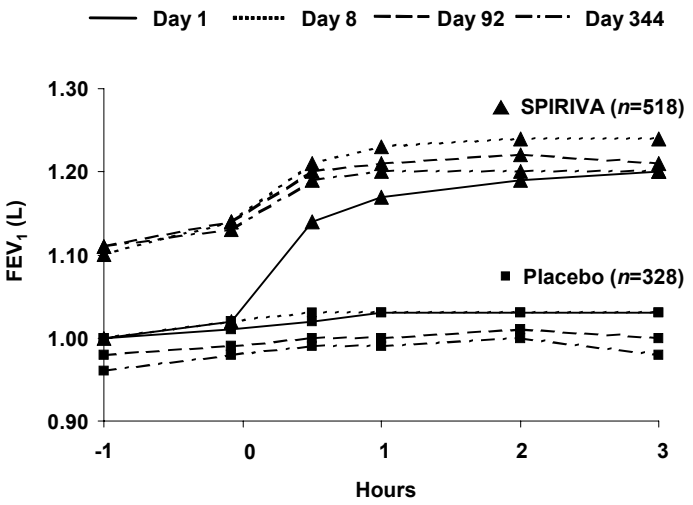
6.2.1 LUNG FUNCTION OUTCOMES IN PIVOTAL PHASE III TRIALS

a. 1-Year Trials: SPIRIVA vs. Placebo

The FEV_1 response for both treatment groups pre-dose (trough) and up to 3 hours following study drug administration on test days 1, 8, 92 and 344 is displayed in figure 6.1. SPIRIVA was associated with a significant increase from baseline FEV_1 compared with placebo ($p<0.01$) post dose on day 1 and pre- and post dose over the one year period.

Pharmacodynamic steady state was reached by day 8. Pre-dose (trough) FEV_1 was significantly greater compared to placebo at day 8, indicating 24 hour duration of action. Mean (±SE) pre-dose (trough) FEV_1 values were increased from baseline compared to placebo for all treatment days. The peak and average FEV_1 post dose was significantly greater in the SPIRIVA group compared to placebo ($p<0.01$).[2,3] Bronchodilation was sustained throughout the 1-year observation period, with no evidence of tachyphylaxis.[2,3]

Figure 6.1: Improvement in FEV_1 Over 1 Year: SPIRIVA vs. Placebo[2,3]



p<0.01 at all time points

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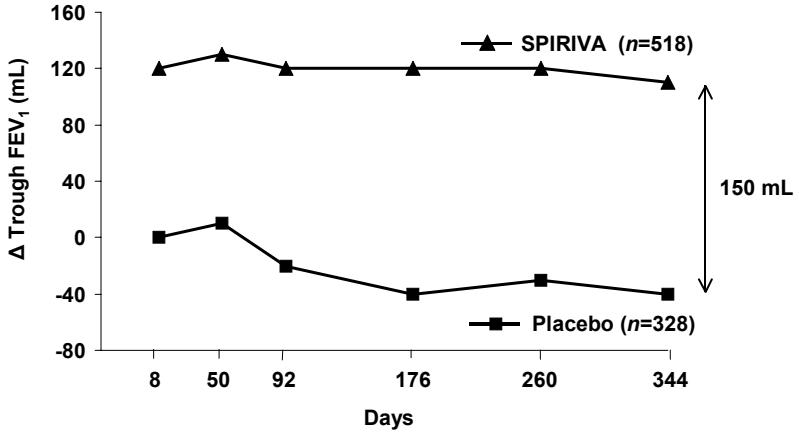
Figure 6.2: Trough FEV_1 Over 1 Year: SPIRIVA vs. Placebo[2,3]



***P*<0.01 at all time points**

Figure 6.2 displays the sustained improvement in pre-dose (trough) FEV_1 (from baseline) compared to placebo from test day 8 to the end of the one year observation period. At the end of the one year study, the mean SPIRIVA trough FEV_1 response was superior to placebo by 120mL±10mL to 150mL±20mL ($p<0.01$; see Figure 6.2).[2] This is consistent with the sustained 24 hour bronchodilation of SPIRIVA.

Subgroup analysis of bronchodilator efficacy was performed according to spirometric severity as determined by baseline percentage of predicted FEV_1. SPIRIVA provided superior bronchodilation compared with placebo throughout the 1-year study in patients with mild, moderate, and severe COPD ($p<0.001$; Table 6.4).[19]

Table 6.4: Difference in Trough and Peak FEV_1 vs. Placebo in Patients With Mild, Moderate, and Severe COPD[19]

Severity (FEV_1 % predicted)	Difference in Trough FEV_1 ± SE (mL)		Difference in Peak FEV_1 ± SE (mL)	
	Day 8	Day 344	Day 8	Day 344
Mild (≥50%)	130 (± 30)	120 (± 30)	210 (± 30)	210 (± 40)
Moderate (35% to <50%)	130 (± 20)	220 (± 30)	240 (± 30)	270 (± 30)
Severe (<35%)	110 (± 20)	120 (± 20)	210 (± 20)	180 (± 30)

p<0.001 for all differences. Differences were calculated as SPIRIVA minus placebo.

Forced Vital Capacity (FVC)

FVC measurements assess the volume of air that can be forcibly expired during maximum exhalation with no limitation to time. Improvements in FVC reflect reductions in air trapping, an important factor in the pathophysiology of dyspnea in COPD.[1]

The pattern of FVC response was similar to that of FEV_1.[2] Sustained improvements in FVC occurred over 1 year with no evidence of tachyphylaxis. SPIRIVA significantly improved pre-dose (trough) FVC compared to placebo, confirming the efficacy of once-daily dosing. The mean increase in trough FVC ranged from 260 to 290mL over baseline, and was 300mL over placebo at the end of the trial (p<0.0001).

In the SPIRIVA group, the average FVC response over 3 hours ranged from 420 to 510mL over baseline, and was significantly better than placebo on day 344 (p<0.0001). The mean peak FVC also showed a statistically significant improvement over placebo at each time point.

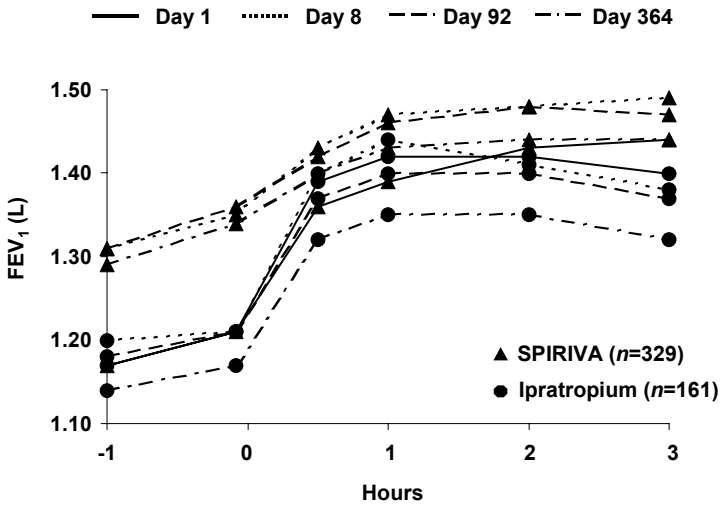
Peak Expiratory Flow Rate (PEFR)

The SPIRIVA treated group demonstrated significantly higher PEFRs compared to placebo, for both morning and evening measurements (p<0.05). Differences in weekly means for morning PEFR ranged from 11±4 to 25±6L/min over the 1-year period.[2]

b. 1-Year Trials: SPIRIVA vs. Ipratropium

The FEV_1 response for both treatment groups (pre-dose and up to 3 hours post dose) on test days from day 1 to day 364, is displayed in Figure 6.3. As was observed in the placebo controlled trials, significant bronchodilation occured within 30 minutes after the first dose of SPIRIVA. On all test days beyond the first day, SPIRIVA resulted in significantly greater trough and peak FEV_1 compared to ipratropium (p<0.05; see Figure 6.3).[3,5]

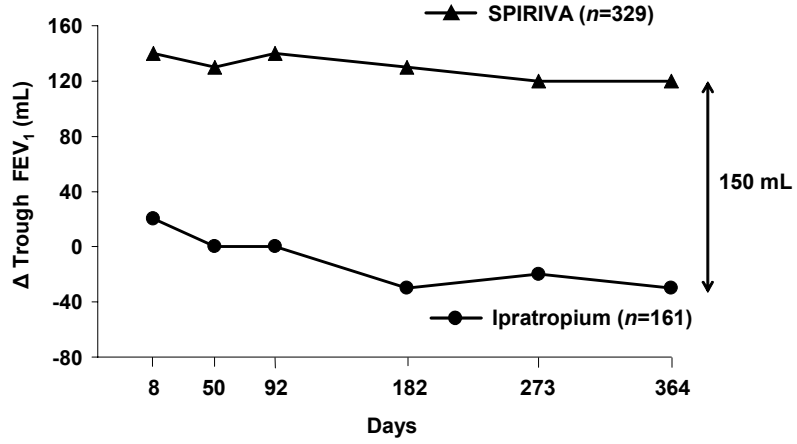
Figure 6.3: Improvement in FEV_1 Over 1 Year: SPIRIVA vs. Ipratropium[3,5]



***P*<0.05 at all time points except day 1, 30-120 minutes posttreatment and day 8, 30-60 minutes posttreatment**

On day 8 (steady state), mean trough FEV_1 was 140mL above baseline in SPIRIVA treated patients—an increase of 12%—compared with only 20mL above baseline in ipratropium treated patients ($p<0.001$). This difference was even more pronounced at the end of 1 year (day 364) with SPIRIVA treatment, with mean trough FEV_1 120mL above baseline, compared with a 30mL decline in FEV_1 from baseline levels with ipratropium treatment—a difference of 150mL between the 2 groups ($p<0.001$; see Figure 6.4).[3,5]

Figure 6.4: Trough FEV_1 Over 1 Year: SPIRIVA vs. Ipratropium.[5]



***P*<0.001 on all test days**

Figure 6.4 notes the mean change in pre-dose FEV_1 (i.e., 23-24 hours following last dose of SPIRIVA) from baseline on test days 8, 50, 92, 182, 273 and 364.

Table 6.5: Difference in Trough and Peak FEV_1 vs. Ipratropium in Patients With Mild, Moderate and Severe COPD[3]

Severity (FEV_1 % predicted)	Difference in Trough FEV_1 ± SE (mL)		Difference in Peak FEV_1 ± SE (mL)	
	Day 8	Day 364	Day 8	Day 364
Mild (≥50%)	170*(± 40)	190*(± 50)	70(± 50)	90(± 50)
Moderate (35% to <50%)	120*(± 30)	150*(± 30)	70*(± 30)	100*(± 40)
Severe (<35%)	110*(± 30)	150*(± 40)	70*(± 40)	110*(± 40)

*p<0.05 SPIRIVA vs. Ipratropium

As shown in Table 6.5 above, a subgroup analysis of bronchodilator efficacy was performed according to spirometric severity. SPIRIVA provided statistically significant increase in bronchodilation compared with ipratropium throughout the 1-year study in all patients with mild, moderate, and severe COPD for trough FEV_1 and for moderate and severe disease for peak FEV_1 ($p<0.05$) .[3]

Forced Vital Capacity (FVC)

The results of the FVC response in the ipratropium trial support the conclusions derived from the FEV_1 data. By day 8, the mean trough FVC response was higher in the SPIRIVA group compared with the ipratropium group. The difference between SPIRIVA and ipratropium was statistically significant ($p<0.05$) at trough on all test days. By the end of study, trough FVC was 320mL above the day 1 baseline for patients receiving SPIRIVA and 110mL above baseline for those receiving ipratropium (with a mean difference of 210mL between groups). While not always statistically significant, peak FVC was higher with SPIRIVA on all test days.

Peak Expiratory Flow Rate (PEFR)

Morning and evening PEFRs were significantly higher with SPIRIVA compared to ipratropium ($p<0.01$ at all weekly intervals).[3,5]

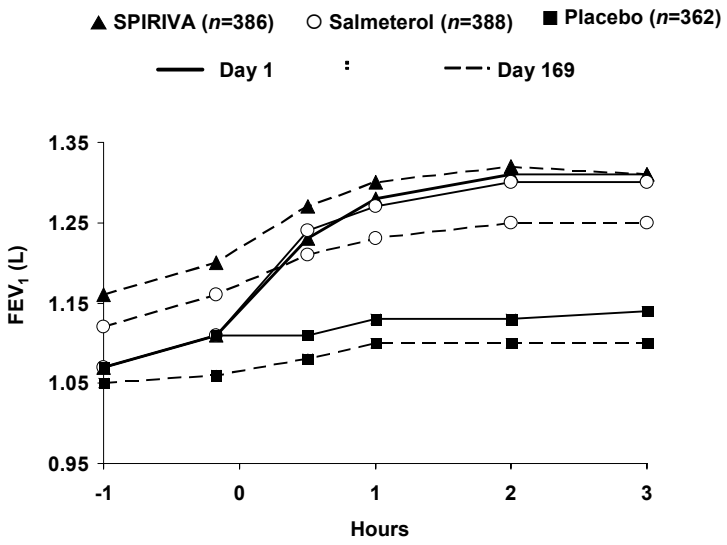
c. 6-Month Trials: SPIRIVA vs. Salmeterol vs. Placebo

The design of the two salmeterol comparison studies was identical, with the exception of the duration of serial spirometry (12 hours in one study and 3 hours in the other). Data from these two studies have been pooled, with the exception of the 12 hour spirometric data which is available from only one study. Average FEV_1 and FVC over the 3 and 12 hour observation periods were estimated by analysis of area under the curve (AUC) for the observation period and standardized for time. This method was chosen because AUC analysis by trapezoidal rule is the most accurate reflection of the average value for a given measurement at any point in time.

3-Hour Spirometry(pooled data from 2 trials)

Figure 6.5 shows that both SPIRIVA and salmeterol were associated with post dose FEV_1 values that were consistently higher than those with placebo ($p<0.01$). SPIRIVA was more effective than salmeterol in improving peak and 3-hour average FEV_1 after 2 weeks of treatment ($p<0.05$) and was sustained throughout the study.[3]

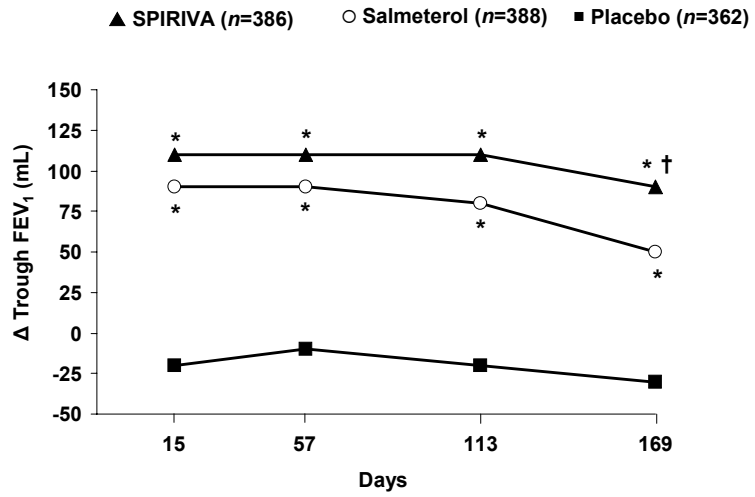
Figure 6.5: Improvement in FEV_1 Over 6 Months (pooled studies, 3-hour spirometry): SPIRIVA vs. Salmeterol vs. Placebo[3,6,7]



***p*<0.01 vs placebo at all time points**
***p*<0.05 vs salmeterol on all test days except days 1 and 15**

The mean change in pre-dose (trough) FEV_1 (i.e., 23-24 hours following last dose of SPIRIVA; 12 hours following salmeterol dose) from baseline is displayed in Figure 6.6. The improvement in trough FEV_1 was significantly greater for both SPIRIVA and salmeterol, compared with placebo, on all test days. At day 169, the SPIRIVA trough response was significantly greater compared to salmeterol. ($p<0.05$).

Figure 6.6: Mean Trough FEV_1 Over 6 Months (pooled studies, 3-hour spirometry): SPIRIVA vs. Salmeterol vs. Placebo[3,6,7]

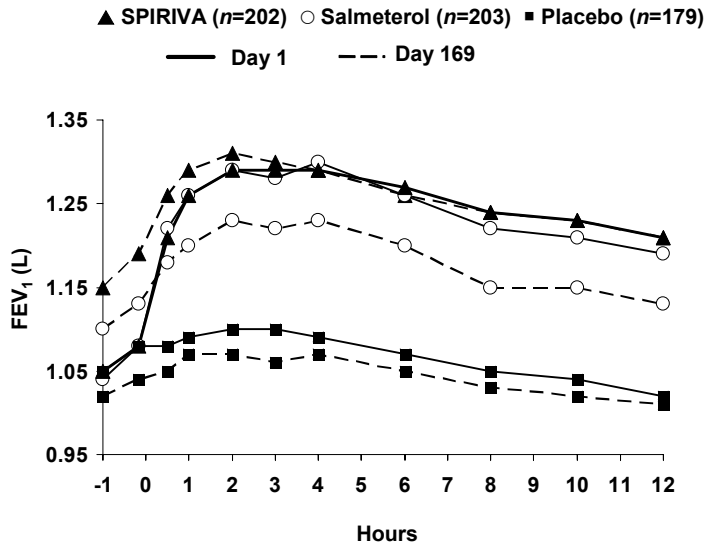


*P<0.001 vs placebo
†P<0.05 vs salmeterol

12-Hour Spirometry

Both SPIRIVA and salmeterol treatment groups demonstrated significantly higher peak and average FEV_1 over 12 hours compared to placebo on all test days ($p<0.001$). SPIRIVA was associated with significantly higher average FEV_1 compared to salmeterol on all test days ($p<0.05$) except days 1 and 15 (see Figure 6.7), with no evidence of tachyphylaxis.[7] At 24 weeks, trough FEV_1 improved significantly over placebo with active treatment (+137mL with SPIRIVA vs. +85mL with salmeterol)—a significant difference between the 2 active drugs ($p<0.01$).[7] Salmeterol was associated with attenuation of bronchodilator response over the 6 month observation period (i.e., tachyphylaxis).[7]

Figure 6.7: Improvement in FEV_1 Over 6 Months (12-hour spirometry study): SPIRIVA vs. Salmeterol vs. Placebo[7]



***P*<0.001 vs placebo on all test days posttreatment**
***P*<0.05 vs salmeterol on all test days except days 1 and 15**

Figure 6.7 notes the FEV_1 response (in liters) for all treatment groups at one hour pre-dose and up to 12 hours following administration on test days 1 and 169.

Forced Vital Capacity (FVC)

In the combined 6-month trials, the FVC responses parallel those observed with FEV_1, with significant improvements in FVC in both active comparators over placebo. SPIRIVA also showed significant improvements compared to salmeterol ($p<0.05$) on all test days except days 1 and 15. At the end of the study, trough FVC was significantly greater in the SPIRIVA group compared to both the placebo ($p<0.001$) and the salmeterol groups ($p<0.001$).

Peak Expiratory Flow Rate (PEFR)

In the combined 6-month trials, AM and PM PEFRs were significantly higher with both SPIRIVA and salmeterol compared with placebo, at all weeks ($p<0.01$). Although morning PEFRs did not differ between the SPIRIVA and salmeterol groups, there was a significant difference favoring SPIRIVA over salmeterol in evening PEFRs at all weeks ($p<0.05$).[3]

6.2.2 DYSPNEA OUTCOMES IN PIVOTAL PHASE III TRIALS

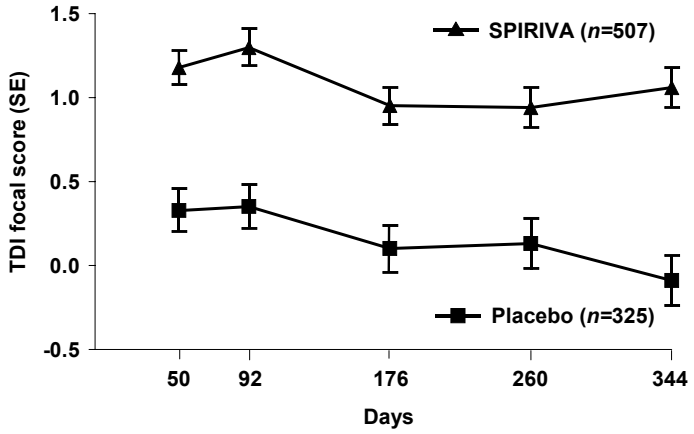
Dyspnea is an important patient-centered outcome, since it is a major determinant of HRQoL and the ability to perform daily activities in patients with COPD.[20-24] In the pivotal phase III trials, dyspnea was evaluated using the BDI, which measures the severity of dyspnea at baseline and TDI, which scores the post-treatment changes in

dyspnea from baseline. See Appendix A-1.2 for additional information on instruments for measuring dyspnea.

a. 1-Year Trials: SPIRIVA vs. Placebo

Mean BDI focal scores (±SE) showed moderate dyspnea in the SPIRIVA and placebo groups[2] (6.03±0.09 and 6.21±0.12, respectively).[3] Significantly higher TDI focal scores, indicative of an improvement in dyspnea, were reported for SPIRIVA compared to placebo on all assessment days ($p<0.001$; Figure 6.8).[2] A change in the TDI focal score of 1 unit has been defined as the minimal clinically important difference for this instrument. The percentage of patients achieving a change in TDI focal score of ≥1 unit was significantly higher in the SPIRIVA group compared to the placebo group on all test days (46% vs. 29% respectively, $p<0.01$).[2] COPD symptom scores for shortness of breath, as recorded in patients' daily diaries, also supported improvements in dyspnea for the SPIRIVA group compared to placebo ($p<0.05$).[2] Improvements in TDI appeared to be sustained during the year study period.

Figure 6.8: TDI Focal Score: SPIRIVA vs. Placebo [2]



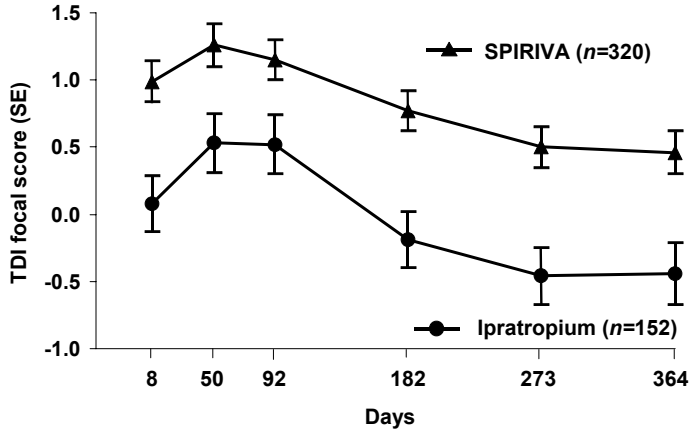
***P*<0.001 on all test days**

Use of rescue bronchodilators is often related to patients' perception of dyspnea and may be indicative of symptom control. At 1 year, mean use of rescue albuterol was significantly lower for SPIRIVA treated patients compared to placebo (3.2±0.11 doses/day vs. 4.1±0.13 doses/day, respectively; $p<0.01$).[2]

b. 1-Year Trials: SPIRIVA vs. Ipratropium

Mean BDI focal scores (± SE) were comparable for the two treatment groups, and indicated moderate dyspnea (7.13±0.14 for SPIRIVA and 7.41±0.19 for ipratropium).[3,5] SPIRIVA was associated with significant improvement in TDI focal score on all test days, as displayed in Figure 6.9 ($p<0.05$).[5] The percentage of patients achieving > 1 unit improvement in TDI focal score at 1 year was significantly higher with SPIRIVA compared to ipratropium (31% vs. 18%, respectively; $p<0.05$).[5]

Figure 6.9: TDI Focal Score: SPIRIVA vs. Ipratropium[3,5]



P<0.05 on all test days

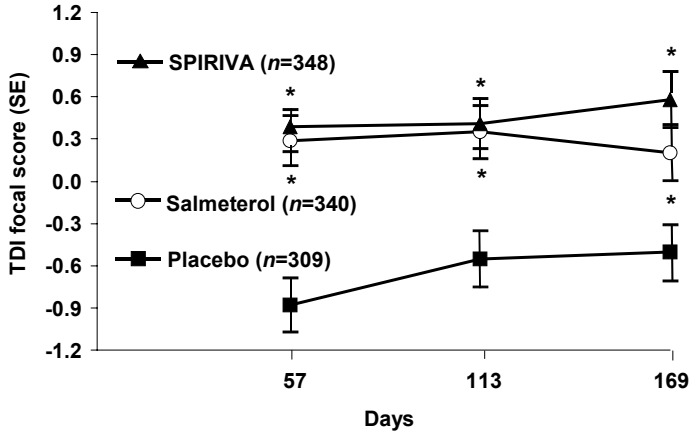
Use of rescue albuterol was reduced with SPIRIVA, with an average of approximately four fewer albuterol inhalations per week in the SPIRIVA group compared to the ipratropium group ($p<0.05$ for all weeks except weeks 1, 4, 34, 36-38, 40, 47, 49, and 50-52).[5]

c. 6-Month Trials: SPIRIVA vs. Salmeterol vs. Placebo

Mean BDI focal scores (±SE) in all groups showed moderate dyspnea (6.55 ± 0.12, 6.55 ± 0.13, and 6.56 ± 0.13 in the SPIRIVA, salmeterol, and placebo groups, respectively).[3] Both SPIRIVA and salmeterol improved TDI focal score from baseline compared to placebo ($p<0.05$; see Figure 6.10), with no significant difference between the 2 active comparators.[6] In addition, 43% of SPIRIVA treated patients and 41% of salmeterol treated patients achieved ≥1 unit improvement in TDI focal score, compared with only 30% of patients receiving placebo ($p<0.01$).[6]

Throughout the study, patients in the SPIRIVA and salmeterol treatment groups reported fewer respiratory symptoms ($p<0.05$) and used less rescue albuterol ($p<0.01$) compared to patients in the placebo group.[3]

Figure 6.10: TDI Focal Score: SPIRIVA vs. Salmeterol vs. Placebo[3,6,7]



**P*<0.05 vs placebo*

Throughout the study, patients in the SPIRIVA and salmeterol treatment groups reported fewer respiratory symptoms ($p<0.05$) and used less rescue albuterol ($p<0.01$) compared to patients in the placebo group.[3]

6.2.3 OUTCOMES IN EXACERBATIONS/HOSPITALIZATIONS IN PIVOTAL PHASE III TRIALS

COPD exacerbations and associated hospitalizations are associated with significant morbidity, mortality, health resources utilization and cost. Studies have shown a strong association between hospitalization for COPD exacerbations and mortality.[25-27] Recent data suggests an association between the frequency of exacerbations and the rate of decline in FEV_1 in patients with COPD.[28,29] The phase III trials evaluated exacerbations and exacerbation-related hospitalizations, with exacerbation data captured by the reporting of adverse events (see Tables 6.6, 6.7, and 6.8). In these trials COPD exacerbation was defined as a complex of 2 or more new or increased respiratory symptoms (including dyspnea, wheeze, cough, sputum production) lasting at least 3 days and reported as an adverse event. It should be noted that although this definition does not require a treatment intervention, approximately 90% of events reported as exacerbations were treated with antibiotics, systemic corticosteroids or both.

a. 1-Year Trials: SPIRIVA vs. Placebo

As summarized in Table 6.6, SPIRIVA was associated with significantly lower rates of exacerbations and hospitalizations, compared to placebo despite use of concurrent respiratory medications such as inhaled steroids and theophyllines as previously prescribed by their physicians and rescue albuterol (provided to all patients).[2] In addition, the percentage of patients using oral steroid medication for COPD exacerbations, was lower with SPIRIVA compared to placebo.[4] In these trials a total of 90 of 550 (16.4%) patients in the SPIRIVA group took oral steroid bursts for the control of COPD exacerbations compared to 92 of 371 (24.8%) patients in the placebo group over the 49-

week treatment period. The difference between the two treatment groups was statistically significant ($p<0.01$).[3]

Table 6.6: Exacerbations and Hospitalizations Due to Exacerbations Over 1 Year: SPIRIVA vs. Placebo[2]

	Incidence of Exacerbations*	Number of Exacerbations per Year†	Incidence of Hospitalizations‡	Number of Hospitalizations per Year†
SPIRIVA	36%§	0.76§	5.5%§	0.09§
Placebo	42%	0.95	9.4%	0.16

* Percentage of patients experiencing ≥1 exacerbation during the 1-year study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 1-year study.
§ $p<0.05$ vs. placebo.

b. 1-Year Trials: SPIRIVA vs. Ipratropium

SPIRIVA was associated with significant reductions in the incidence and number of exacerbations compared to ipratriopium.[5] (Table 6.7). SPIRIVA was also associated with a trend towards a lower incidence and frequency of hospitalizations and number of hospitalizations for exacerbations, although these differences did not reach statistical significance. The percentage of patients using oral steroid medication was lower with SPIRIVA compared to ipratropium.[4] In these trials a total of 78 of 356 (21.9%) patients in the SPIRIVA group took oral steroid bursts compared to 50 of 179 (27.9%) patients in the ipratropium group for the control of COPD exacerbations over the 52-week treatment period. The difference between the 2 treatment groups was not statistically significant ($p=0.133$).[3]

Table 6.7: Exacerbations and Hospitalizations Due to Exacerbations Over 1 Year: SPIRIVA vs. Ipratropium[5]

	Incidence of Exacerbations*	Number of Exacerbations per Year†	Incidence of Hospitalizations‡	Number of Hospitalizations per Year†
SPIRIVA	35%§	0.73§	7.3%	0.10§§
Ipratropium	46%	0.96	11.7%	0.16

*Percentage of patients experiencing ≥1 exacerbation during the 1-year study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 1-year study.
§ $p<0.05$ vs. ipratropium.
§§ $p=0.09$ vs. ipratropium.

c. 6-Month Trials: SPIRIVA vs. Salmeterol vs. Placebo

SPIRIVA significantly reduced exacerbation frequency compared to placebo ($p<0.05$), whereas salmeterol did not. As displayed in Table 6.8, there were trends toward fewer hospitalizations due to exacerbations with SPIRIVA compared to salmeterol and placebo.[6] In these trials, the percentages of patients using oral steroid bursts for exacerbation treatment were 11.2% (SPIRIVA), 13.8% (salmeterol), and 14.5% (placebo), with no significant differences among the treatment groups.[6]

Table 6.8: Mean Incidence of Exacerbations and Hospitalizations Due to Exacerbations Over 6 Months: SPIRIVA vs. Salmeterol vs. Placebo[6]

	Incidence of Exacerbations*	Number of Exacerbations per Year†	Incidence of Hospitalizations‡	Number of Hospitalizations per Year†
SPIRIVA	32%§	1.07§	3%	0.10§
Salmeterol	35%	1.23	5%	0.17
Placebo	39%	1.49	5%	0.15

*Percentage of patients experiencing ≥1 exacerbation/hospitalization during the 6-month study.
† Number of exacerbations/hospitalizations per patient-year.
‡ Percentage of patients experiencing ≥1 hospitalization during the 6-month study.
§ $p < 0.05$ vs. placebo.

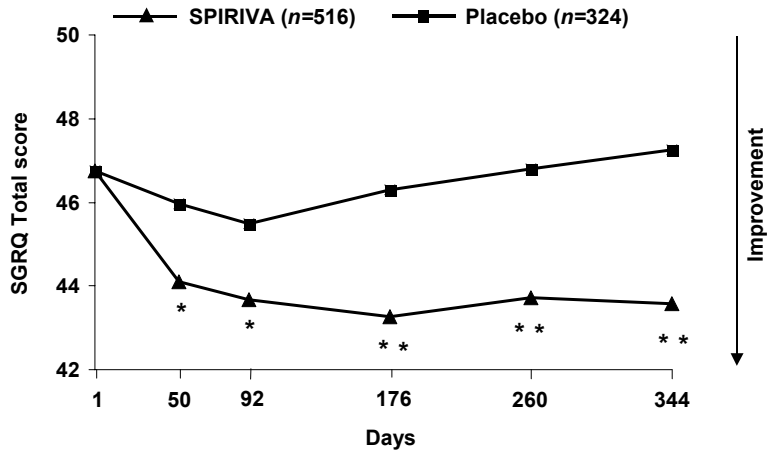
6.2.4 HRQoL Outcomes in Pivotal Phase III Trials

In all the pivotal clinical trials, respiratory HRQoL was evaluated using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ total score reflects COPD symptoms (e.g., dyspnea), activity, and psychosocial impacts of the disease.[30] A 4 unit decrease in the SGRQ total score has been defined as the minimum clinically meaningful difference for this instrument.

a. 1-Year Trials: SPIRIVA vs. Placebo

SPIRIVA demonstrated significant improvement in SGRQ total score compared with placebo on all test days ($p<0.05$; see Figure 6.11). Of SPIRIVA treated patients, 49% achieved at least a 4 unit decrease in SGRQ total score at the end of the study, compared to 30% of those receiving placebo ($p<0.05$).[2,3] Improvements in SGRQ total score appeared to be maintained over the one year treatment period.

Figure 6.11: SGRQ Total Score Over 1 Year: SPIRIVA vs. Placebo[2,3,16]

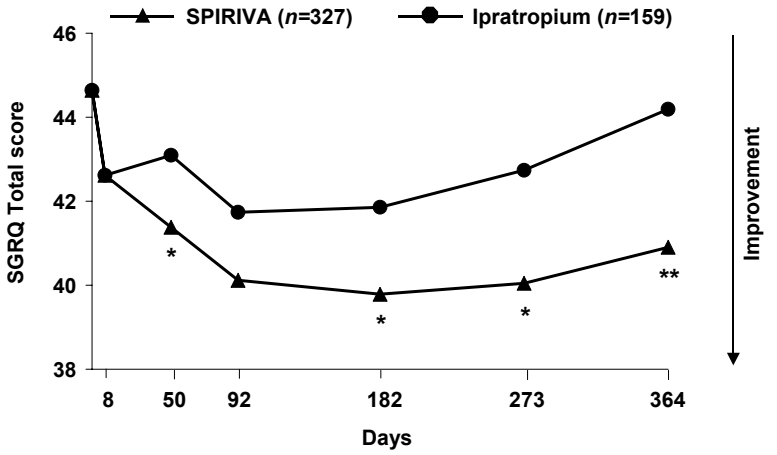


*P<0.05
**P<0.001

b. 1-Year Trials: SPIRIVA vs. Ipratropium

SGRQ total score improved in both treatment groups. However, in the ipratropium group, the score gradually returned to baseline values, whereas improvement with SPIRIVA was sustained over the year of study (see Figure 6.12). More patients in the SPIRIVA group achieved clinically meaningful improvement in SGRQ total score after 9 and 12 months, with 52% of SPIRIVA treated patients achieving this score at 1 year, compared with only 35% of ipratropium treated patients (p=0.001).[3,5]

Figure 6.12: SGRQ Total Score Over 1 Year: SPIRIVA vs. Ipratropium[3,5]

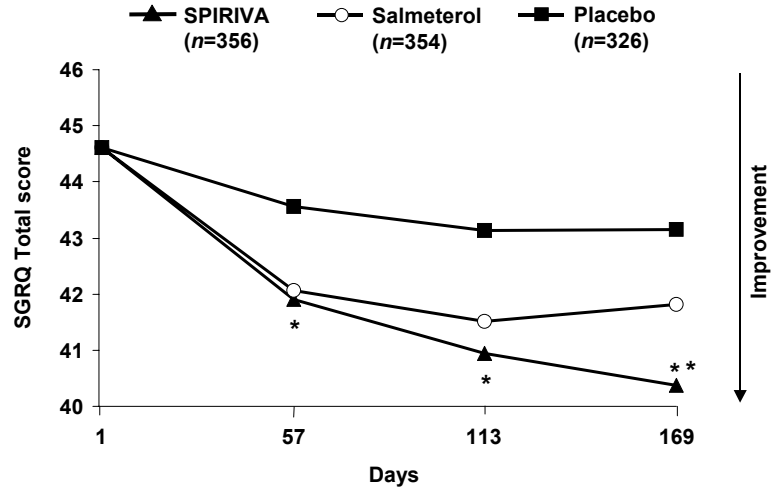


*P<0.05
**P<0.01

c. 6-Month Trials: SPIRIVA vs. Salmeterol vs. Placebo

In the 6-month trials, SPIRIVA significantly improved SGRQ total score at all time points, compared with placebo ($p<0.01$), whereas salmeterol did not. (Figure 6.13). In addition, a higher percentage of patients treated with SPIRIVA achieved a $\geq$ 4 unit decrease in SGRQ total score compared to salmeterol and placebo (48.9% vs. 43.2% vs. 39.3%, respectively; $p<0.05$ for SPIRIVA compared to placebo).[3,6] The improvement with SPIRIVA was maintained over the six month treatment period.

Figure 6.13: SGRQ Total Score Over 6 Months: SPIRIVA vs. Salmeterol vs. Placebo[3,6,7]



*P<0.05 vs placebo
**P<0.01 vs placebo

6.3 Study Designs And Outcomes of Subsequent Trials

a. COPD Exacerbation and Hospitalization Study

Design/Objectives

The principal objective of the study was to prospectively confirm the previous observations of decreased frequency of exacerbations and related hospitalizations with SPIRIVA in the one year pivotal trials. This trial was a 6-month, randomized, double-blind, placebo-controlled, parallel group trial in patients with COPD in the Veterans Affairs (VA) Medical System. The trial was conducted at 26 VA Medical Centers in the United States. In accordance with intent to treat (ITT) principles, patients were encouraged to continue study participation for the entire six month observation period even if trial medication was prematurely discontinued.[31]

Patient Demographics/Treatments

A total of 1,829 patients were randomized into the study. The inclusion/exclusion criteria were less restrictive compared to the pivotal trials in order to allow for inclusion of a broader population of patients with COPD including 29% of patients using home oxygen at entry into the study. During the treatment period, patients were permitted to continue using all of their usual respiratory medications (including LABAs) with the single exception of anticholinergic agents. Treatment groups were randomized to receive SPIRIVA 18µg or identical placebo once daily via the HandiHaler.[31]

Assessments

The incidence and frequency of exacerbations of COPD and hospitalizations for exacerbations were assessed. Health resource utilization, including use of antibiotics and steroids for exacerbations, as well as unscheduled outpatient vists were also evaluated. COPD exacerbations were defined by the presence of two or more respiratory symptoms (increased or new onset) with a duration of at least 3 days, and requiring treatment with antibiotics, steroids or hospitalization.[31]

Results

Baseline demographics are provided in Table 6.9.
The study cohort was predominantly male with a mean age of approximately 68 years. The mean FEV_1 was approximately 1.04L (35.6% of predicted normal), consistent with a population of patients with moderate to severe COPD.

Table 6.9 Patient Demographics for Exacerbations Study[31]

	SPIRIVA 18µg qd	**Placebo***
Randomized (n)	914	915
Age (years, mean)	67.6	68.1
% less than Age 65 years	34.8	30.6
Gender (%)		
Male	98.2	98.8
Female	1.8	1.2
Mean Baseline FEV_1 (L)	1.04	1.04
Mean FEV_1 % predicted	35.6	35.6
FEV_1/FVC (%)	47.9	47.7

***** All randomized patients were provided with albuterol and were permitted to continue use of all previously prescribed respiratory medications (i.e., long-acting beta-agonists, theophyllines, oral and inhaled steroids, antibiotics, and mucolytics) with the exception of anticholinergics during the 6-month observation period; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

A significantly smaller percentage of patients in the SPIRIVA group experienced a COPD exacerbation during the six month treatment period compared with placebo (27.8% vs. 32.3%; 5.7% reduction; p=0.037). Likewise, a smaller percentage of patients in the SPIRIVA group were hospitalized for exacerbations compared to the control

group, however this difference approached but did not reach statistical significance (7.0% vs. 9.5%; 2.5% reduction, p=0.056).[10,31]

Secondary endpoints evaluating exacerbation and related hospitalizations support the above findings. SPIRIVA was associated with a significant reduction in the number of exacerbations and number of exacerbation days. In addition, SPIRIVA was associated with a reduction in the number of hospitalizations (p=0.047) and a reduction in number of hospitalization days (p=0.019). Similar reductions were seen in the number of antibiotic days (p=0.015) and number of unscheduled visits (p=0.019). Hospitalization days and systemic corticosteroid treatment days for an exacerbation did not statistically differ between the two groups, nor did all-cause hospitalizations or all-cause hospitalization days. Table 6.10 reports these data.[31]

Table 6.10 Secondary Endpoints: Exacerbations and Hospitalizations*[31]

	Spiriva (n=914)	Placebo (n-=915)	Difference	p value
# exacerbations	0.85	1.05	- 0.20	0.031
# exacerbation days	12.6	16.0	- 3.35	0.019
# antibiotic days	8.1	9.8	- 1.71	0.015
# steroid days	6.3	7.4	- 1.15	0.25
# unscheduled visits	0.39	0.49	- 0.11	0.019
# hosp due to exac	0.18	0.25	- 0.08	0.047
#hosp days due to exac	1.4	1.7	- 0.27	0.054
#all-cause hosp	0.450	0.510	- 0.05	0.68
#all-cause hosp days	3.7	3.5	0.14	0.77

*# per patient year

Furthermore, time to first exacerbation (p=0.028) was significantly prolonged with SPIRIVA. The time to first hospitalization (p=0.055) was prolonged in the SPIRIVA group, although this relationship was of borderline statistical significance. [10,31]

While previous core clinical trials excluded patients using home oxygen, in this trial they are considered an important subgroup as they generally have more severe COPD and have a greater likelihood of a severe exacerbation. Of the home oxygen using patients, 37% had at least one exacerbation and 13% had at least one COPD related hospitalization compared to 27% and 6% for the corresponding events in patients without home oxygen.[31]

Exacerbations: The MISTRAL Study

The MISTRAL study evaluated the effects of tiotropium on exacerbations of COPD. Using a standard definition and severity classification of exacerbations (somewhat different from the one-year and the six-month core trials), frequency and severity of exacerbations were monitored in a 1-yr, randomized, double-blind, placebo-controlled trial. 1010 COPD patients (mean FEV_1 1.37L, 47.9% pred; age 64.8yrs; 88% men) with a history of at least one exacerbation in the previous year, were randomly assigned to tiotropium 18 μg qd or placebo in 177 centers in France. The primary endpoint for the

trial was morning pre-dose peak expiratory flow rate (PEFR). The primary endpoint and spirometry results were statistically superior to the placebo group. Exacerbations were secondary endpoints and defined as the onset of ≥1 clinical symptom (worsening of dyspnea, cough or sputum production; appearance of purulent sputum; fever of >38ºC or appearance of new chest radiograph abnormalitiy) requiring a new prescription or an increase in the dose of β_2-agonists, antibiotics, corticosteroids or bronchodilators. The severity of an exacerbation was defined as mild, moderate or severe. Mild exacerbations were defined as ≥1 but <3 clinical symptoms. Severe exacerbations were defined as requiring hospitalization OR FEV_1 or PEFR decline >30% of baseline on ≥2 consecutive days OR partial pressure of oxygen (PaO_2) decrease of ≥10mmHg or PaO_2 ≤60mmHg OR partial pressure of carbon dioxide ($PaCO_2$) increase ≥5mmHg or $PaCO_2$ ≥45mmHg. Moderate exacerbations were those considered neither mild nor severe. Results for exacerbation endpoints are found in Table 6.11.

Table 6.11 Exacerbation Reductions in the MISTRAL Study[32]

	Tiotropium	Placebo	Reduction	p-value
Mild, moderate and severe exacerbations				
Patients with ≥1 exacerbation (%)	49.9	60.3	-17%	<0.01
Mean no. of exacerations/yr	1.57	2.41	-35%	<0.01
Mean no. of days of exacerbations/yr	21.1	33.3	-37%	<0.01
Moderate to severe exacerbations				
Patients with ≥1 exacerbation (%)	30.6	43.7	-30%	<0.01
Mean no. of exacerbation/yr	1.06	1.64	-35%	<0.01
Mean no. of days of exacerbations/yr	15.1	23.0	-34%	<0.01

Time to first exacerbation was significantly reduced with tiotropium (p<0.001). The significant effect of tiotropium on reduction of exacerbations was independent of the use of inhaled corticosteroids. In patients receiving inhaled corticosteroids (N=615), incidence of exacerbations was significantly reduced by 29% with tiotropium (1.79 vs 2.52 exacerbations/yr, p=0.0014). In those not on inhaled corticosteroids, the frequency of exacerbations was reduced by 44% with tiotropium (1.24 vs 2.23 exacerbations/yr) but did not reach statistical significance due to the smaller group size (N=388). In conclusion, tiotropium significantly reduced the frequency of COPD exacerbations. This effect was also observed in COPD patients treated with inhaled corticosteroids.[32]

Exacerbations: The SPRUCE Study

SPRUCE (Spiriva Usual Care) evaluated the efficacy and safety of SPIRIVA 18 mcg once-daily via the HandiHaler compared with placebo in a broad, mild to severe COPD primary care population from 48 centers throughout the United Kingdom. The study was a randomized, double-blind, parallel-group, placebo-controlled trial with a duration of 12 weeks. A total of 395 patients were randomized with 200 patients receiving SPIRIVA and 195 receiving placebo in addition to their usual COPD care such as long acting beta 2 agonists and inhaled corticosteroids.

The primary endpoint was trough FEV_1 response. COPD exacerbations were defined as a complex of respiratory events/symptoms with a duration of at least 3 days and required a change in treatment. The change in treatment included a course of antibiotics and/or systemic corticosteroids. The severity of an exacerbation was defined as mild, moderate or severe according to the investigator's clinical opinion. Significantly fewer SPIRIVA patients (n=19; 9.5%) experienced ≥1 COPD exacerbation (all severities) than those receiving placebo (n=35; 17.9%) (p = 0.015).[33]

Exacerbations: The SAFE Study

The SAFE (SPIRIVA Assessment of FEV_1) Study was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in COPD patients living in Canada designed to evaluate the effect of continued smoking on the change in FEV_1 (primary endpoint) after 48 weeks' treatment with SPIRIVA 18mcg daily, compared with placebo. A total of 913 patients were randomized, 605 patients receiving SPIRIVA and 308 receiving placebo, the overall demographic profile was balanced between the two treatment groups.

In addition to efficacy parameters, all adverse events were recorded throughout the study period. COPD exacerbations were defined as a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, sputum purulence, wheezing, dyspnea or chest tightness with a duration of at least 3 days requiring treatment with antibiotics and/or systemic steroids. Exacerbations were classified as mild if they required antibiotic treatment without a visit to a healthcare facility, moderate if they required a visit to an outpatient healthcare facility or treatment with systemic steroids (but not requiring hospitalization), and severe if they required hospitalization. SPIRIVA had no effect on the incidence, duration or severity of COPD exacerbations, incidence and duration of hospitalizations due to a COPD exacerbation, or the number of short courses of antibiotics or oral corticosteroids taken for a COPD exacerbation.[34] The absence of an effect observed in this study may have related to a combination of a higher and earlier discontinuation rate in the placebo group in combination with the market introduction of tiotropium in Canada when the trial was being conducted. This bias would have led to the more severely effected patients (i.e. those predisposed to exacerbations) remaining in the tiotropium but not the placebo group.

b. Daytime Lung Function Study: SPIRIVA and Salmeterol

Design/Objective

This trial was a multiple dose comparison of SPIRIVA and salmeterol in a 12-week, randomized, double-blind, double-dummy, parallel group study in patients with COPD. This trial was conducted in 20 sites in the U.S., and 30 sites located in 7 countries (Italy, Greece, Finland, Portugal, Sweden, Turkey and the U.K.).[35]

The primary objective of the study was to further delineate the daytime bronchodilator efficacy of SPIRIVA compared to salmeterol. Efficacy throughout 12 daytime hours was considered clinically relevant as this is the period during which patients are likely to perform activities of daily living.[35]

Patient Demographics/Treatments

A total of 653 patients were randomized and 583 completed this multinational study. The inclusion/exclusion criteria were similar to the phase III pivotal studies. Treatment groups were randomized to receive Spiriva 18µg once daily via the HandiHaler or salmeterol 50µg (2 puffs of 25µg) twice daily by metered dose inhaler. In addition to study medications, patients were allowed concomitant use of rescue albuterol, theophylline, oral and inhaled corticosteroids, antibiotics, and mucolytics, but not long-acting beta$_2$-agonists (LABAs) and anticholinergics other than study medication.[35]

Assessments

Daytime broncodilator efficacy was assessed through serial spirometric measurements over the 12 hours post administration of study medication. Average FEV_1 and FVC over the 12 hour observation period was assessed by analysis of area under the curve (AUC) for the observation period and standardized for time. This method was chosen because AUC analysis by the trapezoidal rule is the most accurate reflection of the average value for a given measurement at any point in time.[35] Exacerbation data was collected for descriptive purposes, however, the study was not powered to detect a difference in COPD exacerbations between the two treatment groups.[35]

Results

Table 6.12 Patient Demographics for Daytime Lung Function Study[35]

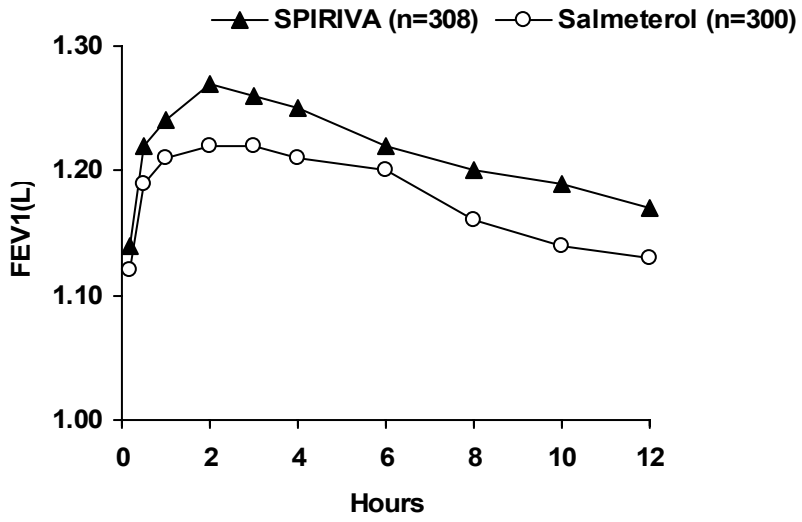
	SPIRIVA 18µg qd	Salmeterol 50µg bid
Randomized (n)	328	325
Age (years, mean)	64.6	68.0
% less than Age 65 years	47	46
Gender (%)		
Male	64.2	64.6
Female	35.8	35.4
Mean Baseline FEV_1 (L)	1.04	1.05
Mean FEV_1 % predicted	37.7	37.6
FEV_1/FVC (%)	43.4	42.7

FEV_1=forced expiratory volume in 1 second;

FVC=forced vital capacity.

The SPIRIVA group demonstrated significantly greater mean peak and average FEV_1 responses compared to the salmeterol group at 12 weeks (see figure 6.14). The SPIRIVA group demonstrated a 46mL greater mean peak FEV_1 response ($p<0.05$) and a 37mL greater average FEV_1 response ($p<0.05$) compared to the salmeterol group. The mean FEV_1 values observed at all time points during the 12 hour testing interval were higher in the SPIRIVA group compared to the salmeterol group.[9,35] Both active treatment groups demonstrated similar trough FEV_1 responses (0.088 and 0.071 L, respectively) at 12 weeks.

Figure 6.14 Mean FEV_1 (L) Over 12 Hours: SPIRIVA vs. Salmeterol[35]



The SPIRIVA treated group exhibited a significantly greater peak FVC response compared to salmeterol with a difference of 120mL ($p<0.05$). Similarly, SPIRIVA demonstrated a higher mean average FVC response over 12 hours compared to salmeterol with a difference of 101mL between the two groups ($p<0.01$). The SPIRIVA group demonstrated significantly higher FVC values at all timepoints at 12 weeks compared to the salmeterol group. The trough FVC response was also significantly greater in the SPIRIVA treated group compared to the salmeterol treated group ($p<0.05$).[9,35]

There was no significant difference between the two treatment groups in incidence of exacerbations, number of exacerbations, number of exacerbation days, or time to first exacerbation. However, in a post-hoc analyses of safety data, there were significantly fewer exacerbations reported as serious adverse events in the SPIRIVA treated group compared to the salmeterol group (0.91% compared to 3.08%; $p=0.038$).[9,35]

Pooled SPIRIVA - Salmeterol Comparison Data

Given the relative infrequency of exacerbations in trials of three to six month duration, a pooled analysis including data obtained from this study, as well as data from the pivotal,

6-month placebo controlled SPIRIVA versus salmeterol comparison studies was conducted. The SPIRIVA group demonstrated numerically fewer exacerbations per patient year compared to salmeterol, however this 13% difference did not reach s..033statistical significance (0.895 vs. 1.033, exacerbations per patient year respectively, p=0.15). A trend in favor of SPIRIVA was also observed with approximately 45% fewer hospitalizations for exacerbations with SPIRIVA compared to salmeterol (0.087 vs. 0.154 hospitalizations per patient year respectively, p=0.09). The lack of statistical significance may in part be related to the overall low frequency of exacerbations in both treatment groups and the shorter duration of therapy compared to the 1-year trials. [36]

c. Exercise Tolerance Studies

Design/Objective

Two 6-week, multicenter, double-blind, randomized, placebo-controlled, parallel group trials were conducted in which the primary endpoint was endurance during cycle exercise testing.

The first study was conducted in 12 centers in 4 countries (United States, Germany, France, and Canada). The trial sought to evaluate the effect of once-daily inhaled SPIRIVA on exercise tolerance, exertional dyspnea and lung hyperinflation in patients with COPD.[12]

Patient Demographics/Treatment

In the first study, a total of 198 patients were randomized. Inclusion/exclusion criteria were similar to those of other pivotal studies, with some differences. In this study and in the other pivotal trials, patients were at least 40 years of age, but in this study patients were also no older than 70 years. In addition, contraindication to exercise was an exclusion criterion, and all patients had documented static lung hyperinflation at entry. Baseline demographic information appears in Table 6.12. Patients in this trial were permitted to take theophyllines, inhaled steroids and modest doses of oral steroids. All patients were provided with albuterol to use as needed; long-acting beta-agonists and inhaled anticholinergics were excluded.[12]

Assessments

In the first trial, numerous assessments were conducted over 6 weeks of treatment. The outcome variables were as follows:

- Endurance time to symptom limitation during exercise[12]
- Body plethysmography to determine functional residual capacity (FRC), total lung capacity (TLC), and residual volume (RV)[12]

- Inspiratory capacity (IC), calculated as TLC minus FRC[12]
- Borg dyspnea scale and TDI[12]

Results

Table 6.13: Patient Demographics for Exercise Tolerance Study[12]

	SPIRIVA 18µg qd	Placebo
Randomization (n)	96	91
Age (years, mean)	61.5	59.4
Gender (%)		
Male	71	77
Female	29	23
Mean BaselineFEV_1 (L)	1.22	1.27
Mean FEV_1 % predicted	41.2	41.1
FEV_1/FVC (%)	46.2	45.5

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

SPIRIVA treatment was associated with a reduction in lung hyperinflation and improvement in FEV_1 and FVC compared with placebo on days 21 and 42 ($p<0.05$). Reduced hyperinflation was confirmed by significant reduction in RV and FRC as well as increases in IC.[12]

Figure 6.15 notes the pre-dose (i.e., 23-24 hours following last dose of SPIRIVA or placebo) residual volume (in liters) on test days 21 and 42. The trough changes indicate 24-hour pharmacologic lung volume reduction with once daily dosing of SPIRIVA.

Figure 6.15: Trough Residual Volume: SPIRIVA vs. Placebo[12]

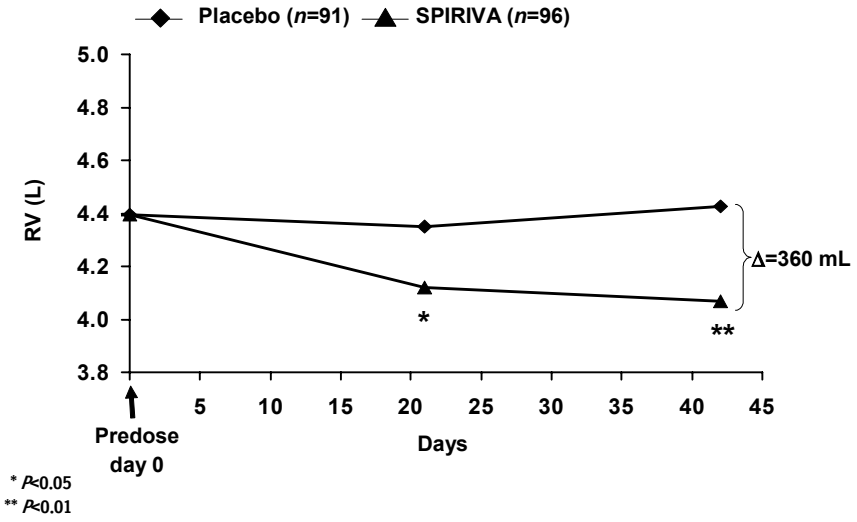
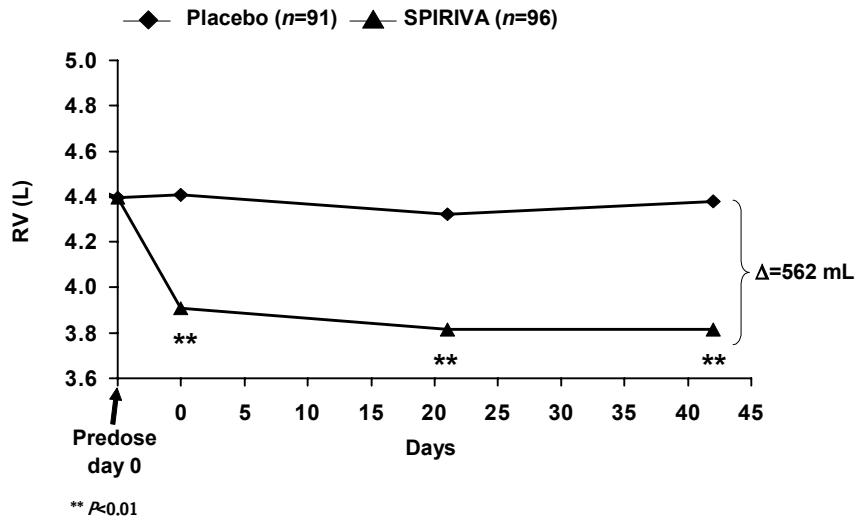


Figure 6.16 notes the peak residual volume (in liters) following administration of SPIRIVA or placebo on test days 0, 21 and 42.

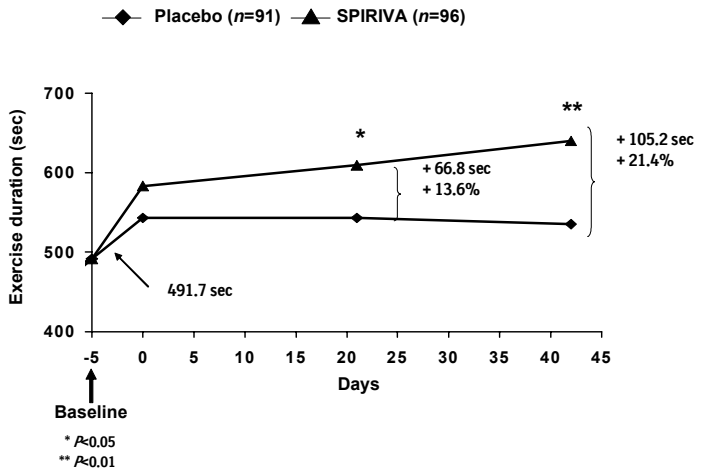
Figure 6.16: Peak Residual Volume: SPIRIVA vs. Placebo[12]



A significant reduction was reported in Borg dyspnea scores in the SPIRIVA group at equivalent exercise times, compared with the placebo group, on all test days. The slope of the increase in Borg dyspnea scores significantly decreased in the SPIRIVA group after 6 weeks of treatment (day 42, $p<0.05$)[12] indicating improvements in the sensation of breathlessness. In addition, the TDI focal score improved by 1.7 units relative to placebo at 6 weeks ($p<0.05$).

Reductions in hyperinflation and exertional dyspnea were accompanied by increased exercise endurance time in this trial. Figure 6.17 notes exercise duration (seconds) following administration of SPIRIVA or placebo at baseline and test days 0, 21 and 42. As depicted, exercise endurance time was significantly improved with SPIRIVA compared to placebo on days 21 and 42 of treatment ($p<0.05$).[12]

Figure 6.17: Exercise Endurance Time: SPIRIVA vs. Placebo[12]



The second international exercise trial which involved 261 patients has recently been published. This randomized, double-blind, placebo-controlled, parallel-group study was conducted in COPD patients with a mean age of 62.5 years, 189 men and 72 women, mean FEV_1 of 1.2 ± 0.4L (43 ± 12.7% predicted). On day 0 (first dose), day 21 and day 42 of treatment, pulmonary function tests were performed before and 1 hour and 20 minutes after dosing, followed by a constant work rate cycle ergometry ts (75% maximum work capacity) to symptom limitation at 2.25 hours after dosing. On day 42, an additional constant work rate cycle ergometry test was performed at 8 hours after dosing. The trial confirmed the pattern of responses observed in the first trial. SPIRIVA improved airflow, reduced hyperinflation and dyspnea and improved endurance time. Adjusted mean pre-exercise inspiratory capacity (IC) on day 42 was 2.41 ± 0.03L (SPIRIVA) versus 2.19 ± 0.03L (placebo) at 2.25 hours after dosing ($p<0.001$), and 2.31 ± 0.03L (SPIRIVA) versus 2.16 ± 0.03L (placebo) at 8 hours after dosing ($p<0.001$). The significant increase in IC with SPIRIVA compared to placebo was maintained throughout exercise. At 42 days endurance time had improved by a mean of 44% (236 seconds) relative to placebo ($p<0.01$). There were two patients who had profoundly prolonged endurance times with SPIRIVA. Even the removal of these two patients still resulted in a mean increase of 31% (164 seconds) relative to placebo ($p<0.01$). [13,14] Furthermore, this study shows that this improvement is present at 2.25 hours and at 8 hours after dosing on day 42 after 6 weeks of treatment. Median increases in exercise tolerance at 2.25 hours after dosing on day 42 (compared to the baseline exercise tolerance on day -5) were 110 seconds in the tiotropium group compared to 10 seconds in the placebo group ($p=0.003$).[13]

The exercise trials illustrate the benefits of SPIRIVA as well as providing a pathophysiologic explanation for these benefits. SPIRIVA improves airflow and reduces hyperinflation thereby permitting patients to increase their ventilation with less breathlessness and, as a result, increase their ability to engage in physical activities longer and more comfortably.[13,14]

The Effect of Pulmonary Rehabilitation on Exercise Tolerance

The combination of SPIRIVA and pulmonary rehabilitation has been shown to improve exercise tolerance.[37] A recent study by Casaburi et al. (*Chest* 2005;127:809-817) showed an improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. The hypothesis was that ventilatory mechanics improvements from tiotropium would permit enhanced ability to train muscles of ambulation and therefore augment exercise tolerance benefits of pulmonary rehabilitation.

In a randomized double blind, placebo-controlled trial (tiotropium, n=47; placebo, n=44), tiotropium 18mcg daily was administered to COPD patients participating in 8 weeks of pulmonary rehabilitation (treadmill training three times a week; ≥ 30 minutes per session) at 17 sites. Study drug was administered 5 weeks prior to, 8 weeks during, and 12 weeks following pulmonary rehabilitation. The primary end point was treadmill walking (0% incline) endurance time at 80% of maximum speed attained in an initial incremental test.

The transition dyspnea index (TDI), St. George's respiratory questionnaire (SGRQ), and rescue albuterol use were secondary end points. The mean age of the 93 participants was 67 years, 57% were men, and mean FEV_1 was 0.88L (34% of predicted).

The mean endurance time difference (tiotropium minus placebo) prior to pulmonary rehabilitation, at the end of pulmonary rehabilitation, and 12 weeks after pulmonary rehabilitation were 1.65 minutes (p=0.183), 5.35 minutes (p=0.025), and 6.60 minutes (p=0.018), respectively. Mean TDI focal scores at the end of pulmonary rehabilitation were 1.75 for tiotropium and 0.91 for placebo (p>0.05). At 12 weeks after pulmonary rehabilitation, TDI focal scores were 1.75 for tiotropium and 0.08 for placebo (p<0.05). Relative to placebo, tiotropium improved SGRQ total scores by 3.86 at the end of pulmonary rehabilitation and 4.44 at 12 weeks after pulmonary rehabilitation (p>0.05). The mean albuterol use declined following pulmonary rehabilitation plus tiotropium, compared to pulmonary rehabilitation alone ($p \leq 0.05$ for 17 of 25 weeks).

In conclusion, tiotropium in combination with pulmonary rehabilitation improved endurance of a constant work rate treadmill task and produced clinically meaningful improvements in dyspnea and health status compared to pulmonary rehabilitation alone. Improvements with tiotropium were sustained for 3 months following completion of pulmonary rehabilitation.[37]

d. AM/PM Dosing: 24-Hour Spirometry Study

Design/Objective

This study was conducted in 8 centers in the United Kingdom and the Netherlands. It was a 6-week, multicenter, double-blind, randomized, placebo-controlled, parallel group trial comparing 24 hour efficacy of both morning and evening SPIRIVA dosing.[3] As with the other aforementioned trials, other respiratory medications were permitted with the exclusion of other inhaled anticholinergics and long-acting beta-agonists.

Patient Demographics/Treatment [3,8]

A total of 121 patients with relatively stable COPD were randomized. Inclusion criteria consisted of an FEV_1 25% to 65% of predicted normal, ≤70% of FVC, age ≥40 years, and a smoking history of ≥10 pack-years. Exclusion criteria consisted of a diagnosis of asthma, allergic rhinitis, atopy or eosinophils ≥600 cells/mm^3. Parallel groups received SPIRIVA 18 µg daily in the AM (n=38), SPIRIVA 18 µg daily in the PM (n=43), or identical placebo (n=40). At baseline all three treatment groups were similar: all were Caucasian with an overall mean age of 65.8 years, 62% of the trial population was male, mean FEV_1 was 1.08L, and mean percent predicted was 40.8%.

Assessments [8]

To assess bronchodilator efficacy, FEV_1 was measured for a full 24 hours at three hour intervals at baseline and at week 6 for for all groups. The primary endpoint, morning

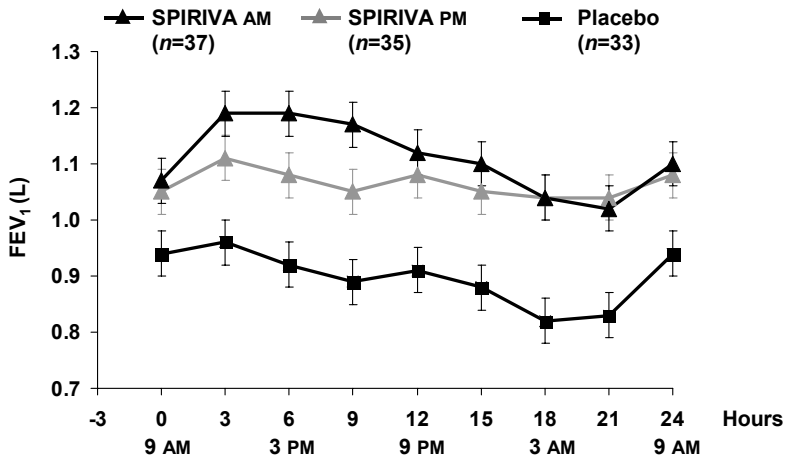
dip, was the mean change from baseline in FEV_1 recorded at 3AM and 6AM on the morning following the last dose of medication on the final study visit. Morning and evening PEFRs were recorded daily on diary cards.

Results

Over the 6-week course of treatment, SPIRIVA produced sustained bronchodilation throughout 24 hours with either morning or evening once-daily dosing. Figure 6.18 shows nocturnal (3AM to 6AM) and steady-state FEV_1 over 24 hours for SPIRIVA dosed

in the morning or evening after six weeks of treatment. Both AM and PM dosing were associated with mean FEV_1 and FVC values that were significantly higher than placebo ($p<0.001$) at all time points. There were no significant differences in lung function between the AM and PM treatment groups.[3,8]

Figure 6.18: SPIRIVA AM/PM Dosing: Improvement in Steady State FEV_1 Over 24 Hours at 6 Weeks



P<0.01 SPIRIVA AM and PM vs placebo (steady state)

During 6 weeks of treatment with SPIRIVA, mean morning and evening PEFRs with either AM or PM dosing were significantly superior to those with placebo ($p<0.02$). In both the AM and PM SPIRIVA groups, mean weekly morning and evening PEFRs increased after 1 week of treatment with the improvements persisting throughout all subsequent treatment weeks.[8]

e. African American Study

In general, COPD patients of African descent have had low representation in industry-sponsored clinical trials. Published data suggest that patients of African descent may have differences in responsiveness to certain pharmacologic agents compared to Caucasian patients. An eight week, randomized, double-blind, placebo controlled, prospective clinical trial was conducted to compare SPIRIVA 18 mcg once daily with

placebo in COPD patients of African descent in the United States. COPD patients ≥ 40 years, FEV_1 ≤ 65% predicted, FEV_1/FVC ≤ 70% with no history of asthma were included. Spirometry (pre-study drug, and 0.5,1,2 and 3 hours postdose) and the University of California San Diego Shortness of Breath Questionnaire (SOBQ) were performed at baseline, and at 4 and 8 weeks. The primary outcome was AM predose FEV_1 at eight weeks. Exacerbations of COPD were captured as adverse events. A total of 166 patients were randomized; 160 were eligible for efficacy evaluation. The mean baseline FEV_1 = 1.02L (41% predicted), age = 62.5 years, males = 67.5%. The number of females in the SPIRIVA group was 20 and in the placebo group was 34. The mean (SE) changes from baseline in spirometry (mL) at eight weeks appear in Table 6.14.

Table 6.14 African American Study Mean (SE) Changes from Baseline (mL) at 8 Weeks

	SPIRIVA (n=78)	**Placebo (n=82)**	**Difference**	**p-value**
Predose FEV_1	156(28)	33(27)	122(39)	0.0022
Peak FEV_1	300(28)	118(27)	182(39)	<0.0001
FEV_1 AUC_{0-3}	208(24)	28(24)	180(34)	<0.0001
Predose FVC	276(46)	7(45)	269(65)	<0.0001
Peak FVC	536(46)	199(45)	336(65)	<0.0001
FVC AUC_{0-3}	364(41)	19(40)	345(58)	<0.0001

The number of patients with COPD exacerbations in the placebo group was twelve and in the SPIRIVA group was zero. There were no significant differences between SPIRIVA and placebo groups in the SOBQ. In conclusion, SPIRIVA significantly improved pulmonary function and reduced COPD exacerbations in COPD patients of African descent.[38]

f. UPLIFT

The purpose of the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial is to determine whether treatment with SPIRIVA reduces the rate of decline of FEV_1 over time in patients with COPD. It is a four year randomized, double-blind, placebo-controlled, parallel group clinical trial involving thirty-seven countries (approximately 475 investigational sites) which has randomized 5,993 patients. The hypothesis was based on observations and post-hoc analyses of the one-year placebo controlled trials in which there appeared to be sustained improvements of lung function over the entire study period relative to the placebo group.[39] The UPLIFT trial is expected to be completed in 2008.

The co-primary endpoints are:

1. The yearly rate of decline in trough FEV_1 from day 30 (steady state) until completion of double-blind treatment. Trough FEV_1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug.

2. The yearly rate of decline in FEV_1 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double-blind treatment.

The secondary endpoints include other derivations of spirometric progression (including FVC and SVC data), the St. George's Respiratory Questionnaire, exacerbations of COPD, hospitalizations for COPD exacerbations, and mortality (respiratory and all-cause).[40]

g. Holter Monitoring Studies

Twenty-four hour Holter monitor data were collected as part of the six-week, multi-center, double-blind, placebo-controlled (n=31) study of SPIRIVA 18 µg inhaled once-daily in the morning (AM, n=37) or evening (PM, n=35) in patients with COPD. Holter studies were performed prior to the first dose and following six weeks of treatment.

Patients remained in the clinic for the duration of the Holter studies. None of the groups showed any substantial difference in heart rate and no conduction problems were observed. Additionally, SPIRIVA was not associated with abnormal supraventricular rhythm disorders and no incidences of atrial flutter or fibrillation were observed.[41]

A prospective 12 week, parallel group, double-blind, randomized, placebo-controlled study involving 196 patients with COPD (100 treated with tiotropium and 96 with placebo) assessed efficacy of SPIRIVA measured by FEV_1 and assessed cardiac safety by measuring 12 lead and Holter ECG monitoring. Tiotropium was not associated with ECG changes in heart rate, rhythm, conduction, or QT intervals based on results from 12-lead and 24-hour Holter monitoring.[42]

h. Efficacy of Salmeterol Plus Fluticasone versus SPIRIVA

A six-week, multicenter, randomized, double-blind, triple-dummy, parallel-group pilot study was conducted to evaluate the spirometric effect size of tiotropium 18mcg daily compared to salmeterol 50mcg twice daily plus fluticasone 250 mcg twice daily in chronic obstructive pulmonary disease (COPD) patients. After 6 weeks of treatment, a 12-hour profile of pulmonary function tests (FEV_1, FVC) was performed. A total of 107 patients were randomized (tiotropium = 56, salmeterol+fluticasone = 51). Randomization failed to provide treatment groups with comparable baseline characteristics (baseline FEV_1: tiotropium 1.31L [n=56], salmeterol + fluticasone 1.47L [n=51]; reversibility (FEV_1 increase of 12% over baseline and 200mL; tiotropium 55.4%, salmeterol + fluticasone 64.7% of subjects). Mean ages (years): tiotropium (62.4); salmeterol + fluticasone (62.5). The primary endpoint was forced expiratory volume area under curve for time period 0 to 12 hours (FEV_1 AUC_{0-12}) at Day 43.

FEV_1 AUC_{0-12} was 1.55±0.03 L in tiotropium and 1.57±0.04 L in salmeterol + fluticasone (95% CI -0.12, 0.07; p=ns; ITT population). Peak FEV_1 was comparable between tiotropium (1.68±0.04 L) and salmeterol + fluticasone (1.66±0.04 L). Trough

FEV_1, although numerically higher in salmeterol + fluticasone, was not significantly different [salmeterol + fluticasone: 1.54±0.03 L; tiotropium: 1.46±0.03 L; 95% CI -0.17, 0.01; p=0.07]. FVC AUC_{0-12} was similar in both arms. Peak FVC and trough FVC were non-significant between groups (peak FVC: salmeterol + fluticasone [3.26±0.07 L]; tiotropium [3.30±0.06 L], p=ns; trough FVC: salmeterol + fluticasone [2.97±0.05 L];tiotropium [2.93±0.05 L], p=ns). Rescue salbutamol use was similar and both treatments were well tolerated. In this underpowered pilot study, in spite of baseline differences between groups favoring salmeterol + fluticasone, tiotropium and salmeterol + fluticasone demonstrated similar efficacy and spirometric profiles over 12 hours in COPD.[43]

i. Improvements of Health Status: The TIPHON Study

The VSRQ is a new, disease specific questionnaire developed by Boehringer Ingelheim, France, to provide investigators with an easier tool for assessment of health status in medical practice than the SGRQ. The VSRQ is based on assigning ratings from a scale of 0 (extreme limitation) to 10 (no limitation) to eight items: shortness of breath, usual daily activities, social life, quality of sleep, pleasure, energy, worry, and sexual life.

This randomized, double-blind, placebo controlled trial is the first with SPIRIVA to assess change in health status, as measured by the St. George's Respiratory Questionnaire, as the **primary** endpoint. The effect of nine months treatment with SPIRIVA inhaled once daily on health status was measured by using both the SGRQ (St. George's Respiratory Questionnaire) and the new VSRQ (Visual Simplified Respiratory Questionnaire). Nine months of treatment with SPIRIVA is considered to be sufficient to evaluate changes in quality of life in COPD. In addition, lung function parameters (FEV_1, FVC, SVC, IC and FIV_1), exacerbations and adverse events were also monitored.

Five hundred and fifty four COPD patients (mean FEV_1 of 1.36L, 46.8% predicted; age 64.2 years; 86.1% men, SGRQ 47.4, VSRQ 45.3) were randomly assigned to SPIRIVA 18mcg daily or placebo in 124 centers in France. At month nine, 59.1% of patients in the SPIRIVA group achieved at least a 4 unit improvement with the SGRQ versus 48.2% in the placebo group (p=0.029). At least a 4 unit change is the accepted minimal clinically important difference. Change from baseline in mean SGRQ total score in the SPIRIVA group was consistently greater than 4 units at each follow up visit. At nine months, change from baseline in VSRQ total score was 6.74 points in the SPIRIVA group compared with 2.35 points in the placebo group. The mean difference between the groups was 4.39 units. Consistent with results obtained with the SGRQ, VSRQ total score in the SPIRIVA group was also improved compared with baseline at each follow up visit and scores were significantly greater at 3 months ($p<0.05$) and 9 months ($p<0.001$) compared with placebo. The minimal clinically important difference for the VSRQ has not been defined.

SPIRIVA significantly improved trough FEV_1, FVC, IC, SVC, and FIV_1 compared with placebo at nine months. The effect of tiotropium on HRQoL was superior to the control

groups in patients who were and who were not receiving inhaled corticosteroids (ICS) during the trial and irrespective of the patients' severity of disease or reversibility status at entry. In summary, maintenance treatment with SPIRIVA provides clinically and statistically significant improvement in the health status of COPD patients.[44]

6.4 DATA SUMMARY: OUTCOMES TRIALS

Table 6.15 Summary Data: Outcomes Trials

Trials	No. of Patients	Design	Lung Function	Dyspnea	Exacerbations/ Hospitalizations	HRQoL	Exercise Tolerance
Phase III Trials							
SPIRIVA 18 µg qd vs. placebo [1-3]	921	Two identical 1-year, multicenter, double-blind, randomized, placebo-controlled trials with data pooled	**FEV_1**: SPIRIVA > placebo† **FVC:** SPIRIVA > placebo†	**TDI focal score:** SPIRIVA > placebo† **% reaching meaningful TDI focal score**: SPIRIVA > placebo† **Reduction in SABA:** SPIRIVA >placebo†	**Exacerbations:** Reduced number with SPIRIVA vs. placebo† **Hospitalizations:** Reduced number with SPIRIVA vs. placebo†	**SGRQ total score**: SPIRIVA greater improvement than placebo† **% reaching meaningful change in SGRQ total score:** SPIRIVA > placebo†	NA
SPIRIVA 18 µg qd vs. ipratropium 40 µg qid [3,5]	535	Two identical 1-year, multicenter, double-blind, randomized, ipratropium-controlled trials with data pooled	**FEV_1**: SPIRIVA > ipratropium† **FVC:** SPIRIVA > ipratropium †	**TDI focal score:** SPIRIVA > ipratropium† **% reaching meaningful TDI focal score**: SPIRIVA > ipratropium† **Reduction in SABA:** SPIRIVA >ipratropium†	**Exacerbations:** Reduced number with SPIRIVA vs. ipratropium† **Hospitalizations:** Similar number with SPIRIVA and ipratropium	**SGRQ total score:** SPIRIVA greater improvement than ipratropium† **% reaching meaningful change in SGRQ total score:** SPIRIVA > ipratropium†	NA
SPIRIVA 18 µg qd vs. salmeterol 50 µg bid vs. placebo[3,6,7]	1,207	Two 6-month, multicenter, double-blind, randomized, placebo-controlled trials. All data pooled, but breakout provided for serial spirometry*	**FEV_1**: SPIRIVA and salmeterol > placebo† **FVC:** SPIRIVA and salmeterol > placebo †	**TDI focal score:** SPIRIVA and salmeterol > placebo† **% reaching meaningful TDI focal score**: SPIRIVA and salmeterol > placebo† **Reduction in SABA:** SPIRIVA >placebo†	**Exacerbations:** Reduced number with SPIRIVA vs. placebo† **Hospitalizations:** Reduced number of hospitalizations with SPIRIVA vs. salmeterol or vs. placebo†	**SGRQ total score:** SPIRIVA greater improvement than placebo† **% reaching meaningful change in SGRQ total score:** SPIRIVA > placebo†	NA
SPIRIVA 18 µg qd vs. salmeterol 50 µg bid (daytime lung function)[35]	653	Multicenter, double-blind, randomized, salmeterol-controlled	**FEV_1**: SPIRIVA > salmeterol † **FVC:** SPIRIVA > salmeterol †	NA	NA	NA	NA

Trials	No. of Patients	Design	Lung Function	Dyspnea	Exacerbations/ Hospitalizations	HRQoL	Exercise Tolerance
Exacerbation Trials							
SPIRIVA 18 µg vs. placebo (Exacerbation/ Hospitalization Trial VA)[30]	1829	6 mo. ,multicenter, double-blind, randomized, placebo-controlled	NA	NA	**Exacerbations:** Reduced number with SPIRIVA vs. placebo† **Hospitalizations:** Reduced number with SPIRIVA vs. placebo†	NA	NA
SPIRIVA 18 µg vs. placebo (MISTRAL Trial, France)	1010	1 year, multicenter, randomized, double-blind, placebo-controlled	NA	NA	**Exacerbations:** Reduced number with SPIRIVA vs palcebo†	NA	NA
SPIRIVA 18 µg vs. placebo (SPRUCE Trial, UK)	395	12 week, multicenter, randomized, double-blind, parallel-group, placebo-controlled	NA	NA	**Exacerbations:** Reduced number with SPIRIVA vs palcebo†	NA	NA
SPIRIVA 18 µg vs. placebo (SAFE Trial, Canada)	913	48-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled	NA	NA	**Exacerbations:** No difference between SPIRIVA vs palcebo	NA	NA
Exercise Tolerance Trials							
SPIRIVA 18 µg qd and exercise tolerance[12,]	198	6-week, multicenter, double-blind, randomized, placebo-controlled	**FEV_1, FVC:** SPIRIVA>placebo† **RV, IC, FRC (hyperinflation):** SPIRIVA>placebo†	**Borg scale:** SPIRIVA>placebo† **TDI focal score:** SPIRIVA>placebo†	NA	NA	**Endurance time:** SPIRIVA>placebo† **IC during exercise (hyperinflation):** SPIRIVA>placebo†
Exercise tolerance improvement over 8 hours[13]	261	6-week, multicenter, double-blind, randomized, placebo-controlled	**FEV_1, FVC:** SPIRIVA>placebo† **RV, IC, FRC (hyperinflation):** SPIRIVA>placebo†	**Borg scale:** SPIRIVA>placebo†			**Endurance time:** SPIRIVA>placebo† **IC during exercise (hyperinflation):** SPIRIVA>placebo†
Pulmonary Rehabilitation Trial	91	25-week, multicenter, double blind, randomized, placebo-controlled		**TDI focal score:** SPIRIVA>placebo† (12 weeks after pulmonary rehab)		**SGRQ total score:** SPIRIVA>placebo (at end of & 12 wks after pulmonary rehab)	**Endurance time:** SPIRIVA>placebo† (at end of & 12 wks after pulm rehab)

Trials	No. of Patients	Design	Lung Function	Dyspnea	Exacerbations/ Hospitalizations	HRQoL	Exercise Tolerance
HRQoL Trials							
TIPHON Trial[44]	554	9 mo , multicenter, double-blind, randomized, placebo-controlled	**FEV_1, FVC:** SPIRIVA>placebo† **IC (hyperinflation):** SPIRIVA>placebo†		**Exacerbations:** Reduced number with SPIRIVA vs palcebo	**SGRQ & % reaching meaningful change:** SPIRIVA > placebo† **VSRQ:** SPIRIVA > placebo	

*One study performed 3-hour spirometry and one performed 12-hour spirometry.
HRQoL=health-related quality of life; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; TDI=transition dyspnea index; SGRQ=St.George's Respiratory Questionnaire; VSRQ=Visual Simplified Respiratory Questionnaire; NA=not applicable; RV=residual volume; IC=inspiratory capacity; SABA=short-acting beta-agonist (albuterol); >=greater improvement; † $p< 0.05$

6.5 HEALTH RESOURCE UTILIZATION SUPPORTING DATA

a. Analysis of Health Resource Utilization for SPIRIVA Compared With Ipratropium Based on the Pooled Clinical Trial Data

A 1-year prospective analysis evaluated data from 2 randomized, controlled, double-blind, double-dummy, parallel-group trials comparing SPIRIVA 18µg inhalation capsules administered once- daily in the morning via the HandiHaler (n=356) with 2 puffs of 20µg of ipratropium administered 4 times per day via the metered dose inhaler (MDI) (n=179) in patients with COPD.[5]

Missing data due to premature withdrawal are a common problem in the analysis of longitudinal data in clinical trials and may have an impact on the results of an economic evaluation, particularly in cases in which there is a difference in the rate of dropouts between groups. To account for this issue, a multiple-imputation method was applied to the clinical trial data to obtain more reliable estimates of health resource utilization.[45]
All resource use, including all-cause hospital admissions (ICU and non-ICU days), emergency room visits, unscheduled visits to pulmonologists, visits to general practitioners and other healthcare providers, pulmonary function tests, imaging tests, laboratory tests, puffs of rescue medication (albuterol, 1 puff = 100µg), and concomitant medication was recorded prospectively.[45]

The mean resource utilization per patient was consistently lower in patients treated with SPIRIVA. Patients receiving SPIRIVA had 45% fewer hospital admissions compared with ipratropium (0.13 vs. 0.24, respectively; $p< 0.03$) Approximately 11% of the patients in the SPIRIVA group and 19% in the ipratropium group had at least one hospital admission ($p=0.03$). This decrease in the number of hospitalizations resulted in 42% fewer inpatient hospital days in the SPIRIVA group compared with the ipratropium group (1.72 vs. 2.98, respectively; $p= 0.07$). There was no statistically significant difference in the number of ICU days between the two groups. SPIRIVA patients had 36% fewer unscheduled visits compared to ipratropium patients (2.04 vs. 3.18, respectively; $p= 0.04$).

b. Analysis of Health Resource Utilization for SPIRIVA Compared With Salmeterol Based on the Pooled Clinical Trial Data

A 6-month prospective analysis evaluated SPIRIVA compared with salmeterol based on the data from two randomized, controlled, double-blind, double-dummy, parallel-group trials comparing SPIRIVA 18µg inhalation capsules administered once daily in the morning via the HandiHaler (n=402) with salmeterol 50µg administered twice daily via a metered dose inhaler (MDI) (n=405) and placebo (n=400) in patients with airway obstruction due to COPD.[6,7] The design of the two trials was similar and the analysis is based on the combined data.

All resource use, including all-cause hospital admissions (ICU and non-ICU days), emergency room visits, unscheduled visits to pulmonologists, visits to general practitioners and other healthcare providers, pulmonary function tests, imaging tests, laboratory tests, puffs of rescue medication (albuterol, 1 puff=100μg), and concomitant medication was recorded prospectively.[6]

The mean resource utilization per patient data showed a consistent pattern of lower resource use in patients treated with SPIRIVA.[6] Patients receiving SPIRIVA had 40% fewer hospital admissions compared to patients receiving salmeterol (0.18 vs. 0.30, respectively; p=0.09). Approximately 3% of the patients in the SPIRIVA group and 5% in the salmeterol group had at least one hospital admission. The lower number of hospitalizations resulted in 27% fewer inpatient hospital days in the SPIRIVA group compared to patients in the salmeterol group (0.76 vs. 1.04, respectively). In addition, SPIRIVA patients had 50% fewer ICU hospital days compared to the salmeterol patients (0.03 vs. 0.06, respectively) Similarly, SPIRIVA patients had 26% fewer non-ICU hospital days compared to salmeterol patients (0.73 vs. 0.98, respectively). SPIRIVA patients had 7% fewer unscheduled visits compared to salmeterol patients (0.91 vs. 0.98 respectively). A consistent trend showing less health resource utilization was present in the SPIRIVA group; however, the differences did not reach statistical significance.[46]

Overall, SPIRIVA resulted in significantly less healthcare resource use compared to ipratropium. In addition, there was a consistent trend toward lower resource use among patients receiving SPIRIVA compared to patients using salmeterol.[46]

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PHARMACOECONOMIC IMPACT MODEL REPORT

7.1 OVERVIEW OF SPIRIVA PHARMACOECONOMIC EVALUATIONS

The pharmacoeconomic evaluation of SPIRIVA consists of two analyses which demonstrate the cost-effectiveness and total budget impact of SPIRIVA. Data from the core clinical program were used to develop a Markov model to estimate the cost-effectiveness of SPIRIVA over a one-year time frame.[1,2] The model estimates the chronic obstructive pulmonary disease (COPD)-related cost per patient per year for SPIRIVA compared to relevant treatment alternatives (ipratropium and salmeterol). In this model the cost-effectiveness measure of *cost per exacerbation avoided* is used to estimate the economic value of SPIRIVA relative to these treatment comparators.

In addition to this base case model, although there have been no clinical trials directly comparing SPIRIVA to the fixed combination of fluticasone propionate 250µg and salmeterol 50µg inhalation powder (Advair 250/50 Diskus), this agent was recently approved for the management of COPD associated with chronic bronchitis; and therefore, may also be considered a relevant treatment comparator. Therefore, several assumptions have been made in the model in order to estimate the cost-effectiveness of SPIRIVA in comparison to Advair 250/50.

Data from these cost-effectiveness analyses have been incorporated into a total budget impact model to evaluate the overall budget impact of SPIRIVA on the maintenance treatment of COPD over a three-year time horizon. This budget impact analysis includes other anticholinergics, long-acting beta$_2$-agonists (LABA) and Advair. Total budget impact is reported in terms of both medical and pharmacy related expenditures.

7.2 SPIRIVA PHARMACOECONOMIC MARKOV MODEL

7.2.1 INTRODUCTION

A one-year trial-based Markov model was developed by Oostenbrink and colleagues at the Institute of Medical Technology Assessment (iMTA), Erasmus University, Rotterdam, Netherlands.[1,2] The base case analysis was structured to combine the estimates of treatment effectiveness with resources consumed and associated costs for each disease severity state to estimate the cost-effectiveness of SPIRIVA compared with ipratropium and salmeterol. This basic framework of the model was adapted to the United States by incorporating local costs and health care resource utilization estimates. This model reflects a prevalence-based managed care perspective and can be customized for health plans using plan-specific data according to their patient population, resource use, and cost characteristics.

7.2.2 TREATMENT COMPARATORS AND TRIAL CHARACTERISTICS

The base case model is structured to evaluate SPIRIVA in comparison to two active treatment comparators, ipratropium and salmeterol, based on data from the clinical trials.[1-5]

- **SPIRIVA**: 18µg inhalation administered once daily via the HandiHaler®
- **Ipratropium**: 2 puffs of 20µg administered four times daily via a metered dose inhaler
- **Salmeterol**: 2 puffs of 25µg administered twice daily via a metered dose inhaler

Data from the core clinical program consisting of six pivotal studies (two one-year placebo controlled, two one-year ipratropium controlled, and two six-months salmeterol and placebo controlled trials) were used to develop the Markov model.[3-5] These studies are discussed in detail in Section 6. In summary, these trials were multi-center, randomized double-blind, double-dummy (where appropriate), parallel group studies designed to evaluate pulmonary function, rate of exacerbations, quality of life, and dyspnea in patients taking SPIRIVA compared with placebo and active treatment comparators (ipratropium and salmeterol).[3-5] These studies included COPD patients with relatively stable airway obstruction who were at least 40 years of age and had a smoking history of more than ten pack-years. In addition, patients with a history of asthma or any significant disease other than COPD that would compromise the patient's ability to participate for the duration of the study were excluded. These studies were similar in design, with the major difference being the study duration (six vs. twelve months).

Data from the six pivotal studies were pooled to calculate the probability of patients transitioning from one disease severity state to another as well as the probability of experiencing an exacerbation in the SPIRIVA treatment arm.[1-5] Similarly, probability inputs for the ipratropium and salmeterol arms were derived from pooled clinical trial data. The model evaluates active treatment comparators, and thus a placebo arm is not included in the pharmacoeconomic analyses.[1,2] The primary cost-effectiveness measure in this analysis is *cost per exacerbation avoided,* which is based on the difference in COPD-related cost per patient per year (numerator) and the difference in number of exacerbations per year (denominator).

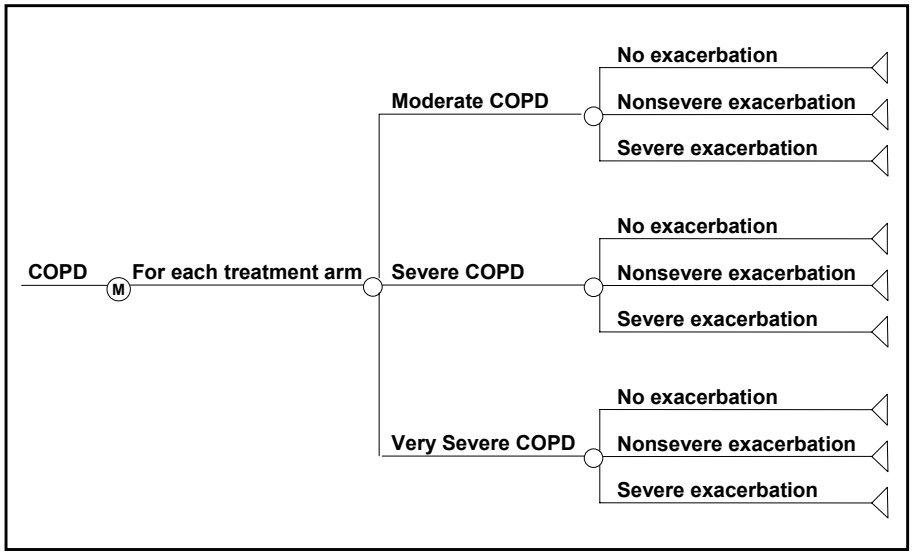
7.2.3 STRUCTURE OF THE MARKOV MODEL

A Markov model is "useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once." [6] Therefore, a Markov model is well-suited to model a chronic disease such as COPD, in which patients can be classified according to disease severity by objective criteria and run a continuous risk of experiencing an exacerbation.[1,2]

The Markov model describes the movements of patients through different disease severity states over time based on the initial distribution among severity states and on the

probability of a transition from one severity state to another over a defined period (*i.e.*, the Markov cycle).[1,2] Depending on the severity state, patients have a certain probability of experiencing an exacerbation. The base case model enables the direct comparison of SPIRIVA, ipratropium, and salmeterol and is primarily driven by disease severity states and exacerbations.[1,2] Figure 7.1 illustrates the simplified graphic representation of the Markov model.[1,2]

Figure 7.1. Simplified graphic representation of the Markov model



Adapted from Oostenbrink, ERS abstract; 2002.

Disease severity states used in the model are based on FEV_1 % predicted and are adapted according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1,2,7]

- **Moderate COPD**: $50\% \leq FEV_1 < 80\%$ predicted
- **Severe COPD**: $30\% \leq FEV_1 < 50\%$ predicted
- **Very Severe COPD**: $FEV_1 < 30\%$ predicted

Although the GOLD guidelines recommend using the postbronchodilator forced expiratory volume in one second (FEV_1) for severity assessment, prebronchodilator values were used because the primary analyses of the trial data were conducted using predose FEV_1 values and postbronchodilator values were not available for all patient visits (a requirement for calculation of transition probabilities based on postbronchodilator values). Therefore, the disease severity states were defined by the prebronchodilator FEV_1 % predicted (*i.e.*, predose FEV_1 values).[1,2]

Patients were included in the core clinical trials if they had a baseline $FEV_1 \leq 65\%$ of predicted normal ($\leq$ 60% of predicted in the 6 months trials) and thus did not include patients with mild COPD (*i.e.,* FEV_1 % predicted > 80%).[3-5] Therefore, "mild" disease is

not included as a severity state in this model.[1,2] Because the number of deaths reported during each of the trials was small [12 (2.3%) in the ipratropium controlled trials, 13

(1.1%) in the salmeterol controlled trials and 2 (0.2%) in the placebo controlled trials], and because the model duration is one year, death is not included as a health state in this model .[3-5]

In the clinical trials, exacerbations were collected as adverse events and were defined as a complex of respiratory symptoms (*i.e.*, new onset or worsening of more than one symptom, such as cough, sputum, dyspnea, or wheeze) lasting for three or more days.[3-5] Exacerbation severity was based on a clinical assessment and was defined as mild, moderate or severe.[1,2]

- **Mild**: awareness of a sign or symptom that is easily tolerated
- **Moderate**: discomfort enough to cause interference with usual activity
- **Severe**: incapacitating or causing inability to do work or usual activity

Mild and moderate exacerbations were combined into one category and defined as nonsevere exacerbations.[8] Therefore, at the end of each Markov cycle, patients had a probability of experiencing either no exacerbation, a nonsevere exacerbation, or a severe exacerbation.[1,2] Based on observations of the ipratropium controlled trials, of the 364 exacerbations that occurred in the studies, only ten patients experienced more than one exacerbation within the same month. As a result, a Markov cycle with a duration of one month was selected and the assumption was made that patients did not experience more than one exacerbation during each cycle.[1,2] All Markov cycles had a duration of one-month except the first cycle, which had a duration of eight days. This eight day cycle, which represents steady state for SPIRIVA, was incorporated to model the initial improvement in pulmonary function that was observed in all studies within the first eight days following the start of study medication.[1,2]

7.2.4 MODEL PARAMETERS

Model inputs include the distribution of patients in each disease severity state at baseline, transition probabilities, probabilities for experiencing an exacerbation (classified as nonsevere or severe), resource use and unit costs.[1,2]

The proportion of patients in each disease severity state at baseline in the model are based on the distribution of patients observed in the ipratropium controlled studies (25% of patients in Moderate COPD, 50% in Severe COPD and 25% in Very Severe COPD).[1,2,5]

Based on FEV_1 measurements at baseline and subsequent follow-up visits from the clinical studies, patients were classified into disease severity states at each visit (Moderate COPD, Severe COPD or Very Severe COPD).[3-5] The frequency distribution over disease severity states that was observed in the studies was used to calculate the

transition probabilities between the disease severity states for the eight-day and one-month Markov cycles.[1,2] Subsequently, the transition probabilities from the different studies were combined to create one set of probabilities for each treatment arm. For SPIRIVA, the transition probabilities are based on the weighted average of the probabilities of the SPIRIVA arms of the six comparator studies. For ipratropium and salmeterol, the transition probabilities are based on the relative difference to SPIRIVA.[1,2]

Since the duration of the salmeterol controlled studies was six months and the duration of the ipratropium and placebo controlled studies was one year, it was assumed that the monthly transition probabilities in the salmeterol controlled studies remained constant for the second half of the year.[1,2] Oostenbrink and colleagues based this assumption on the lack of observed differences (except for differences observed in the first cycle) in the monthly transition probabilities over time in all trials (*i.e.,* the monthly transition probabilities in the ipratropium and placebo controlled studies for the second half-year were similar to the monthly transition probabilities in the first half-year following the first cycle).[1,2] Table 7.1 contains the calculated disease severity state transition probabilities used in the base case model.[1,2]

Table 7.1 Disease severity state transition probabilities, based on trial data (in %)

Transition probabilities for SPIRIVA						
TO ⇒	**Moderate COPD**		**Severe COPD**		**Very Severe COPD**	
FROM ⇓	First cycle	Subsequent cycles	First cycle	Subsequent cycles	First cycle	Subsequent cycles
Moderate COPD	90.7	95.7	9.2	4.0	0.1	0.3
Severe COPD	25.9	2.3	71.6	95.4	2.5	2.3
Very Severe COPD	1.0	0.1	34.1	4.5	64.9	95.4
Transition probabilities for ipratropium						
TO ⇒	**Moderate COPD**		**Severe COPD**		**Very Severe COPD**	
FROM ⇓	First cycle	Subsequent cycles	First cycle	Subsequent cycles	First cycle	Subsequent cycles
Moderate COPD	74.0	92.3	25.8	7.3	0.2	0.4
Severe COPD	10.2	1.3	84.2	95.0	5.6	3.7
Very Severe COPD	0.5	0.2	22.0	2.5	77.5	97.3
Transition probabilities for salmeterol						
TO ⇒	**Moderate COPD**		**Severe COPD**		**Very Severe COPD**	
FROM ⇓	First cycle	Subsequent cycles	First cycle	Subsequent cycles	First cycle	Subsequent cycles
Moderate COPD	90.0	92.9	10.0	6.6	0.0	0.5
Severe COPD	20.1	2.3	76.6	91.8	3.3	5.9
Very Severe COPD	0.0	0.6	30.2	3.6	69.8	95.8

Data collected at each scheduled follow-up visit were used to determine the number of exacerbations since the previous visit and the number of patients in each disease severity state.[3-5] These data were first used to determine the probability of experiencing an exacerbation at each visit and, subsequently, these numbers were recalculated to determine monthly probabilities. Finally, exacerbation probabilities from the different studies were combined to create one set of probabilities for each treatment arm.[1,2] This methodology was similar to the calculation of the disease severity state transition probabilities. Table 7.2 contains the monthly exacerbation probabilities used in the base case model.[1,2]

Table 7.2 Exacerbation probabilities (per month), by disease severity state (in %)

	SPIRIVA		Ipratropium		Salmeterol	
	Nonsevere	Severe	Nonsevere	Severe	Nonsevere	Severe
Moderate COPD	4.7	0.5	5.7	2.3	5.6	0.2
Severe COPD	6.6	1.1	8.0	1.9	7.8	1.3
Very Severe COPD	8.7	2.0	9.3	2.1	9.2	2.4

A linear estimation of the Markov probabilities was created using an Excel model. These probabilities were then applied to the appropriate resources based on whether they were used for maintenance treatment or management of exacerbations. Further details regarding this methodology are described in Appendix 3.

In the model, resource use and cost inputs are structured along disease severity state and exacerbations. Therefore, costs associated with maintenance treatment are reported for each disease severity state and costs related to exacerbations vary for nonsevere and severe exacerbations.[1,2] A crucial assumption within this model is that resource use estimates for maintenance treatment of stable disease and exacerbations within each severity category do not differ between treatment arms. In other words, resource use estimates depend on disease severity state and the severity of the exacerbation, but in a given disease severity state and exacerbation severity, similar estimates are used in each treatment arm. Therefore, apart from the cost of study medication, the differences between treatment groups only result from the transition probabilities between disease severity states and exacerbation probabilities that were derived from the clinical trial data.[1,2] It is important to note that this results in conservative estimates for cost differences between treatment arms, since reduced costs due to better symptom control in the more efficacious treatment are not considered.

COPD-related resource use and unit costs were estimated for the following five categories:

- Cost of maintenance treatment in Moderate COPD
- Cost of maintenance treatment in Severe COPD
- Cost of maintenance treatment in Very Severe COPD
- Cost of nonsevere exacerbation
- Cost of severe exacerbation

Costs related to exacerbations were estimated for nonsevere and severe exacerbations. The model can be customized for health plans using plan-specific data according to their patient population, resource use, and cost characteristics.

- Proportion of patients (*e.g.,* proportion of patients hospitalized)
- Resource use per patient (*e.g*., number of outpatient visits to general practitioner, mean length of ICU stay for hospitalized patients)
- Unit costs (*e.g*., cost of influenza vaccination, cost per day for an ICU stay)

Table 7.3 contains the resource use inputs for maintenance therapy for each disease severity state. Outpatient visits, spirometry, and influenza vaccinations resource utilization estimates were based on assumptions of treatment patterns in the United States. Estimates for outpatient visits were derived from published data by Halpern and colleagues, indicating that two-thirds of COPD patients are treated by a general practitioner, whereas one-third receive care from a specialist.[9] Data from a retrospective managed care database analysis indicate that patients have an average of four visits to a general practitioner each year, while patients seeing a pulmonary specialist average 5.5 visits each year.[10] Based on these data and the fact that the GOLD guidelines state that "visits to health care facilities will increase in frequency as COPD progresses," the number of outpatient visits increase with advancing disease severity.[7] The model assumes that each patient will receive an influenza vaccination annually. In addition, the GOLD guidelines recommend that a patient's decline in lung function is best tracked by periodic spirometry measurements once per year, unless there is a substantial increase in symptoms or a complication.[7] Therefore, in the model it was assumed that patients receive one spirometry test per year. Resource use for maintenance medications were obtained from the U.S.-based placebo controlled studies and reflects the proportion of patients receiving short-acting beta$_2$-agonists, theophylline and inhaled steroids during the treatment period of the study.[3]

Table 7.3 Mean Resource Use for Maintenance Therapy by Disease Severity State (per year)

	Moderate COPD		Severe COPD		Very Severe COPD	
	% of Patients	Resource Use per Patient*	% of Patients	Resource Use per Patient*	% of Patients	Resource Use per Patient*
Outpatient Visit to GP	100.0%	3	70.0%	4	30.0%	6
Outpatient Visit to Pulmonologist	0.0%	0	30.0%	4	70.0%	6
Spirometry	100.0%	1	100.0%	1	100.0%	1
Influenza vaccination	100.0%	1	100.0%	1	100.0%	1
Short-acting beta$_2$-agonists	98.4%	291	97.3%	286	96.3%	279
Theophylline	9.4%	321	15.1%	276	21.6%	280
Inhaled steroids	39.6%	285	42.5%	278	46.0%	278

* Resource use for medications is expressed as number of days

Certain data inputs for resource use related to nonsevere and severe exacerbations were not available from the U.S.-based placebo controlled studies. Therefore, the proportion of patients experiencing a nonsevere or severe exacerbation, and resource use inputs for emergency room visits, exacerbation-related outpatient visits and medication use were obtained from the ipratropium controlled clinical trials, which were conducted in the Netherlands and Belgium.[5,11] A key assumption in this model was that the hospitalization rates for nonsevere and severe exacerbations, as well as resource use associated with management of these exacerbations, were similar to those expected in the U.S. Exacerbation-related medications included antibiotics and oral steroids, assuming that maintenance airway medication use continued as prescribed.

Based on data reported in the literature and observed in U.S.-based trials, it was apparent that the average length of stay (LOS) for hospitalizations associated with these exacerbations in the ipratropium controlled trials was much higher than LOS estimates in the U.S. Thus, hospital LOS data based on U.S. practice patterns were incorporated into the base case model. Maintaining an assumption that there are no treatment-related differences in LOS, average total LOS inputs were derived from the Veteran's Administration (VA) exacerbation trial (see Section 6.3.a.).[12] This study population was predominantly male with a mean age of about 68 years. The mean FEV_1 was approximately 1.04 L (35.6% of predicted normal), consistent with a population of patients with moderate to severe COPD. The objective of the VA exacerbation trial was to prospectively evaluate the efficacy of SPIRIVA in reducing the incidence and frequency of COPD exacerbations and associated hospitalizations. Patients who had a hospitalization with a general ward stay only had an average LOS of 5.68 days.[13] Therefore, in the model 8.23% of patients with a non-severe exacerbation and 66.7% of patients with a severe exacerbation were assigned an average LOS of 5.68 days. In the VA study, patients with an ICU stay as part of their hospitalization had an average LOS of 4.3 days in the ICU and 5.57 days in the general ward.[13] Therefore, these LOS inputs were assigned to the 11.1% of patients with a severe exacerbation. These average total LOS data for exacerbation-related hospitalizations are consistent with other findings.[14-16] Overall, resource use was greater for severe exacerbations than for nonsevere exacerbations, mainly due to the differences in inpatient hospitalizations (Table 7.4).

Table 7.4 Mean Resource Use for Nonsevere and Severe Exacerbations (per event)

	Nonsevere Exacerbation		Severe Exacerbation	
	% of Exacerbations with Resource Use	Resource Use*	% of Exacerbations with Resource Use	Resource Use*
Inpatient (ICU stay)				
ICU cost per day	0.00%	0	11.10%	4.3
General ward cost per day	0.00%	0	11.10%	5.57
Inpatient (General ward stay)				
General ward cost per day	8.23%	5.68	66.70%	5.68
Emergency room				
Emergency room visit	2.87%	1	25.00%	1
Outpatient visits				
General practitioner	45.50%	1.45	44.40%	1.58
Pulmonologist	36.30%	0.94	47.20%	1.74
Other healthcare provider	3.80%	7.11	13.90%	3.6
Medications				
Antibiotics	71.30%	11.13	75.00%	15.67
Systemic steroids	48.40%	15.99	77.80%	30.96

ICU = intensive care unit
* Resource use for medications is expressed as number of days

U.S.-based unit cost data for resource use related to maintenance treatment and exacerbations were obtained from various sources. Cost inputs for exacerbation-related hospital days and emergency room visits were obtained from a database analysis of 215 hospitals.[16] This database represented over 2.5 million annual inpatient visits. Hospital and emergency room charges during calendar year 2000 were identified for admissions with a principal diagnosis of COPD and were converted to costs using cost-to-charge ratios. Based on the results, the cost per day in the ICU in year 2000 was estimated to be $1619.14, the cost per day in the general ward was $1,170.18 and an emergency room visit was $554. Within the model, these costs were adjusted to 2004 dollars using the medical care component of the consumer price index (CPI), as reported in Table 7.5.[17,18] Costs for outpatient visits (for both maintenance treatment and those visits related to an exacerbation) and spirometry were based on the National Fee from the 2004 Physicians' Fee Reference using CPT-4 codes.[19] The cost for an influenza vaccination included both the cost of the vaccine and a professional fee for administration (based on the 50% Physicians' Fee Reference value) and was estimated at $31.87.[19,20] The daily costs for concomitant COPD-related medications were calculated based on the average daily dose of commonly used products in each of the medication categories using 2004 average wholesale price (AWP) for branded products and HCFA pricing for generics.[20] Daily costs for SPIRIVA, salmeterol, and ipratropium were calculated using 2004 AWP and are based on dosages used in the clinical studies.[21] Although the salmeterol controlled studies used salmeterol metered-dose inhaler (MDI), the MDI is no longer available in the United States; therefore, the model uses the daily cost for salmeterol Diskus and assumes that the Diskus has the same efficacy as the MDI.[21] Table 7.5 reflects unit costs in 2004 US dollars.

Table 7.5 Unit Costs in 2004 US Dollars

Inpatient Care	Cost
ICU cost per day	$1,914.23
General ward cost per day	$1,383.44
Emergency room visit	$654.97
Outpatient Services for Maintenance Treatment	
General practitioner (CPT 99213)	$52.65
Pulmonologist (CPT 99214)	$82.14
Spirometry (CPT 94010)	$32.48
Influenza vaccination[1] (CPT 90658)	$31.87
Outpatient Services for Exacerbations	
General practitioner (CPT 99214)	$82.14
Pulmonologist (CPT 99215)	$119.11
Other health care provider (CPT 99211)	$21.28
Medications for Maintenance Treatment (per day)	
Short-acting $beta_2$-agonists	$0.60
Theophylline	$0.74
Inhaled steroids	$2.32
Medications for Exacerbations (per day)	
Antibiotics[2]	$5.05
Systemic steroids[3]	$0.13
Study Medications (per day)†	
SPIRIVA HandiHaler	$4.00
Ipratropium MDI	$2.50
Salmeterol Diskus	$3.38

[1] Includes cost of vaccine and professional fees for administration (PFR 50%)
[2] Based on average treatment with amoxicillin, azithromycin and levofloxacin
[3] Based on average daily dose of oral prednisone 20mg
† Daily cost based on dosages used in the clinical trials

Finally, the Markov model reports the following outcomes:

- Cost per patient per year for each treatment group (reported by inpatient, outpatient and pharmacy costs)
- Estimation of clinical and economic benefits of SPIRIVA over alternative agents (expressed as *cost per exacerbation avoided*)

7.3 CLINICAL TRIALS: SAFETY AND EFFICACY

The clinical trials with SPIRIVA have been reported in detail in Section 6 of this dossier. SPIRIVA (tiotropium bromide inhalation powder), an anticholinergic agent with long-acting muscarinic receptor antagonist activity, was approved by the US Food and Drug

Administration on January 30, 2004. SPIRIVA is indicated for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. In multiple comparative clinical trials, SPIRIVA 18µg administered once daily significantly improved post-dose pulmonary function versus all comparators. This improvement in lung function was maintained without any evidence of tachyphylaxis over a one-year period. SPIRIVA was also shown to provide relief from the symptoms of dyspnea, improve HRQoL, and reduce the number of COPD exacerbations and associated hospitalizations.

Of the 2,663 patients who were enrolled in controlled clinical trials, 1,308 were treated with SPIRIVA at the recommended dose of 18µg once daily. The most commonly reported adverse drug reaction was dry mouth, which was usually mild and often resolved during continued treatment. Other reactions reported in individual patients, consistent with possible anticholinergic effects, included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention. The safety profile of SPIRIVA is described in detail in Section 4.7 of this dossier.

7.4 INCIDENCE AND PREVALENCE IMPACT ASSESSMENTS

The framework of the SPIRIVA cost-effectiveness model, as applied to a chronic disease, is prevalence-based. The cost-effectiveness model represents the relevant treatment pathways over 12 months. As previously mentioned, baseline severity distributions used in the model are based on the distribution of patients observed in the ipratropium controlled trials (Moderate COPD = 25%; Severe COPD = 50%; Very Severe COPD = 25%).[1,2,5]

7.5 PRESENTATION OF BASE CASE MODEL RESULTS

7.5.1 RESULTS OF THE ONE-YEAR TRIAL-BASED MARKOV MODEL

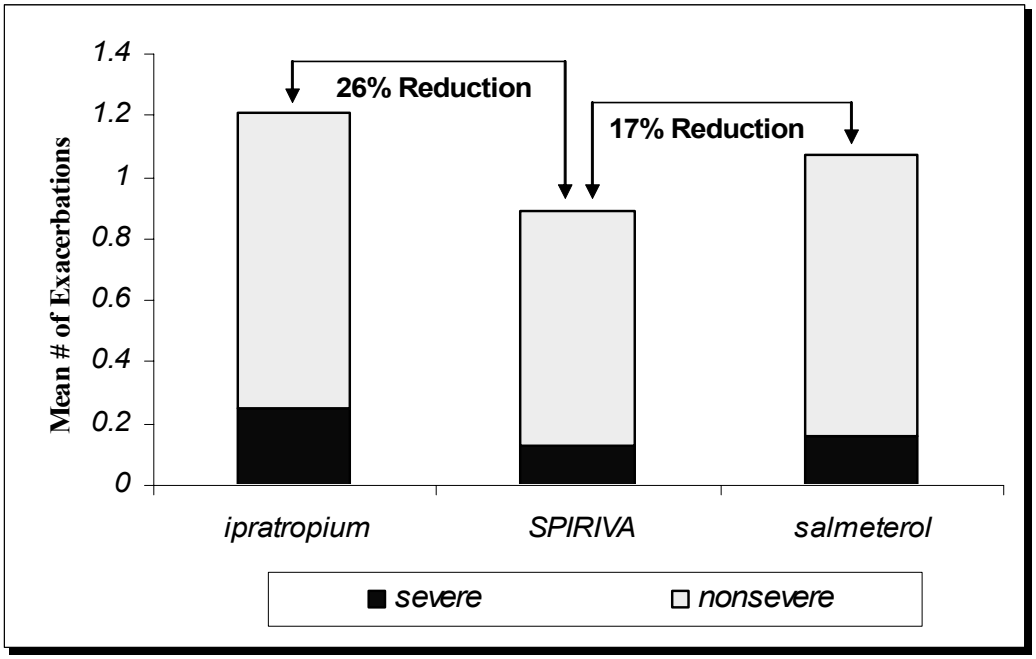
Based on the model inputs, disease severity state transition probabilities, and exacerbation probabilities described above, following one year of treatment, a greater proportion of patients in the SPIRIVA group remained in the less-severe disease states accompanied by less time spent in the more severe disease states (shown in Table 7.6).[1,2]

Table 7.6 Distribution of patients after 12 months – base case analysis

	SPIRIVA	Ipratropium	Difference	Salmeterol	Difference
Distribution of patients among COPD disease states after 12 months					
Moderate COPD	31.73%	15.01%	16.72%	23.25%	8.48%
Severe COPD	47.30%	48.72%	-1.42%	39.82%	7.48%
Very Severe COPD	20.97%	36.27%	-15.30%	36.93%	-15.96%
Months in COPD disease states at month 12					
Moderate COPD	4.02	2.26	1.76	3.28	0.74
Severe COPD	5.64	6.17	-0.53	5.22	0.42
Very Severe COPD	2.34	3.57	-1.23	3.50	-1.16

Based on the results, patients treated with SPIRIVA had a lower number of severe and nonsevere exacerbations compared with patients treated with ipratropium or salmeterol. As shown in Figure 7.2, the annual mean number of exacerbations was 0.89 in the SPIRIVA group, versus 1.21 in the ipratropium group and 1.07 in the salmeterol group.[1,2]

Figure 7.2 Annual number of exacerbations per patient – SPIRIVA compared with treatment alternatives

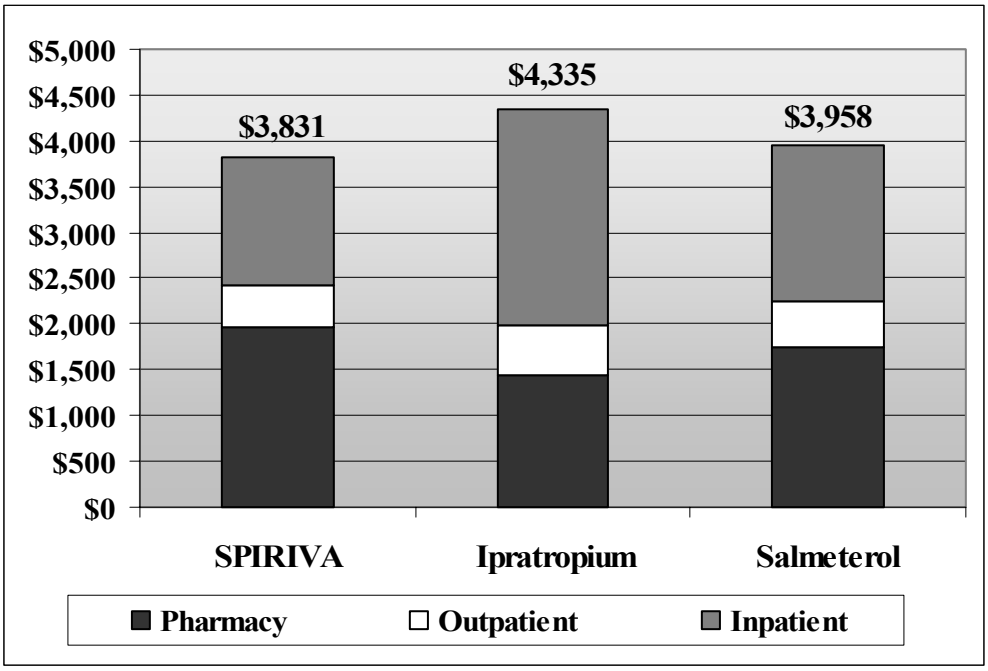


The annual mean number of severe exacerbations in the SPIRIVA group was reduced by 48% and 19%, relative to ipratropium and salmeterol, respectively. Similarly, the mean number of nonsevere exacerbations over one year was reduced in the SPIRIVA group by 21% relative to ipratropium and 16% relative to salmeterol. As a result, the total number of exacerbations in the SPIRIVA group was 26% and 17% lower relative to ipratropium and salmeterol, respectively. A consistent pattern of lower resource use was observed in

patients treated with SPIRIVA. The internal consistency of the model was evaluated by incorporating probabilities specific to each trial (*i.e.,* the ipratropium controlled studies) and comparing the model results with the clinical trial results. The results of this model validation demonstrated only small deviations between the clinical trials and model results.[1,2]

Mean total cost per patient from the one-year model was $3,831 in the SPIRIVA group, $4,335 in the ipratropium group, and $3,958 in the salmeterol group (Figure 7.3). The higher pharmacy expenditures associated with SPIRIVA are fully offset by savings in total medical expenditures. Specifically, the total medical costs (outpatient and inpatient) over one year were less in the SPIRIVA group than in the ipratropium and salmeterol groups, resulting in a total medical cost savings of $1,031 and $342, respectively.

Figure 7.3 Cost per Patient per Year, by Cost Component ($US)



Finally, an estimate of the *cost per exacerbation avoided* was -$1,575 when compared with ipratropium and -$706 when compared with salmeterol (Figure 7.4). The negative incremental cost-effectiveness ratios indicate that SPIRIVA is less costly and more effective than ipratropium and salmeterol (*i.e.,* dominant). Thus, for every exacerbation avoided by using SPIRIVA, this positive health outcome occurs at a cost savings compared with ipratropium and salmeterol. Table 7.7 summarizes the results of the cost-effectiveness analysis.

Figure 7.4 Cost per Exacerbation Avoided – Comparators relative to SPIRIVA ($US)

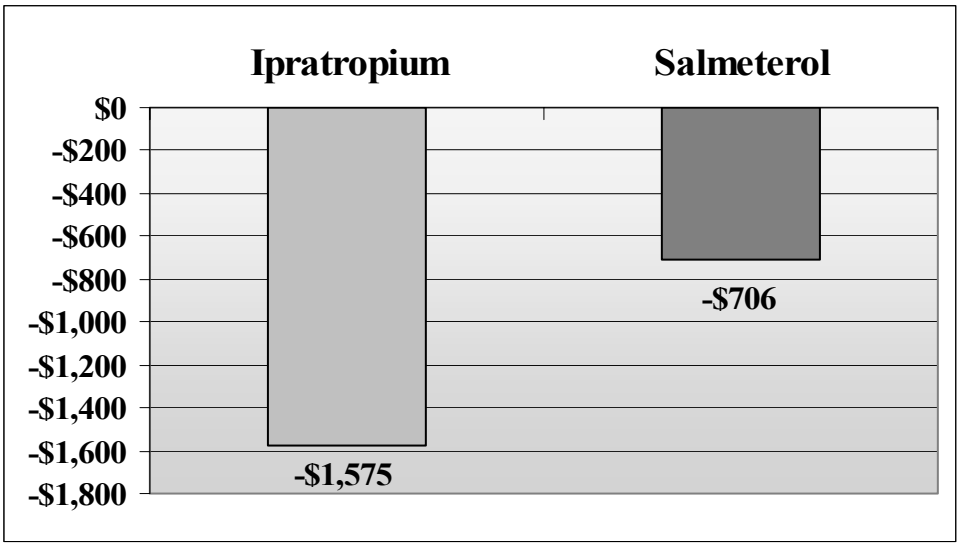


Table 7.7 Exacerbations, Total Costs and Cost-Effectiveness Ratios ($US)

	SPIRIVA	Ipratropium	Difference	Salmeterol	Difference
Exacerbations					
Severe	0.13	0.25	-0.12	0.16	-0.03
Nonsevere	0.76	0.96	-0.2	0.91	-0.15
Total	0.89	1.21	-0.32	1.07	-0.18
Pharmacy	$1,972	$1,445	$527	$1,757	$215
Outpatient	$450	$542	-$92	$500	-$50
Inpatient	$1,409	$2,348	-$939	$1,701	-$292
Total Costs	**$3,831**	**$4,335**	**-$504**	**$3,958**	**-$127**
Cost per exacerbation avoided			**-$1,575**		**-$706**

In summary, the base case analysis of the SPIRIVA pharmacoeconomic model demonstrates that SPIRIVA is dominant to ipratropium and salmeterol (*i.e.,* SPIRIVA is less costly and more effective than ipratropium and salmeterol); and thus, SPIRIVA is a cost-saving alternative to ipratropium and salmeterol for the maintenance treatment of COPD. Therefore, using SPIRIVA for the maintenance treatment of COPD will not result in overall increased costs and will be associated with improved effectiveness compared with using ipratropium or salmeterol. It is important to note that SPIRIVA also provides additional health benefits such as improvements in dyspnea, HRQoL, and exercise tolerance. Any cost offsets associated with these additional benefits are not factored into this Markov model.

7.5.2 INCLUSION OF ADVAIR 250/50 IN THE MARKOV MODEL

Advair Diskus 250/50 was approved in November 2003 for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.[22] Advair Diskus 250/50 was the only dose strength that received approval. The higher dose (*i.e.,* Advair Diskus 500/50) was not approved and specifically not recommended for the treatment of COPD.[22] It is anticipated that this new indication will result in increased market share for Advair in the treatment of COPD. Although the indication is specific to those COPD patients with chronic bronchitis, it is important to consider Advair 250/50 in the cost-effectiveness model and budget impact analysis. No direct comparison data exist for SPIRIVA versus Advair 250/50; therefore, several assumptions were made in order to evaluate the cost-effectiveness of SPIRIVA compared to Advair 250/50. The assumptions regarding the efficacy of Advair 250/50 were derived from FDA submission documents and the Advair package insert.[22,23]

- Although the clinical data showed improvements in lung function (as defined by predose and postdose FEV_1) that were significantly greater with Advair 250/50 than with salmeterol, data from study SFCA3007 indicate that the highest incidence of COPD exacerbations occurred in the fluticasone 250µg and Advair 250µg/50µg groups, while the lowest occurred in the salmeterol 50µg group.[23] The proportions of patients experiencing one or more COPD exacerbation were as follows: 37% in the salmeterol group, 39% in the placebo group, 40% in the Advair 250/50 group and 43% in the fluticasone group. Based on the study criteria for determining the severity of an exacerbation, 31% of patients in the salmeterol group, 34% of patients in the placebo and Advair 250/50 groups and 38% of patients in the fluticasone group had moderate/severe exacerbations.[23] In addition, data from the package insert specified that Advair 250/50 did not demonstrate a significant reduction in chronic bronchitis symptoms or in COPD exacerbations compared to placebo over 24 weeks of therapy.[22] Therefore, since exacerbations are the primary economic endpoint in this cost-effectiveness analysis, Advair 250/50 was assumed to have equivalent efficacy to salmeterol, implying no additional resource use benefits for Advair 250/50 over salmeterol. All transition probabilities, probabilities for exacerbations and resource use inputs for the salmeterol arm were applied to Advair 250/50.

- Based on the package insert, Advair 250/50 has not been evaluated in patients with COPD associated with chronic bronchitis for periods longer than six months.[22] However, in this analysis, Advair 250/50 treatment was assumed to continue for one year in the cost-effectiveness model and annually in the budget impact analysis.

- The package insert recommends that "patients who are treated with Advair Diskus 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment."[22] This includes patient monitoring of bone mineral

density changes and regular eye examinations to detect problems such as cataracts or glaucoma.

- "Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD). …Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended, including prior to instituting ADVAIR DISKUS 250/50 and periodically thereafter."[22]

- "Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS; therefore, regular eye examinations should be considered."[22]

In the model, assessment of bone mineral density changes with a dual energy x-ray absorptiometry (DEXA) scan of the pelvic bone was assumed to occur once a year during Advair 250/50 treatment. In addition, it was assumed that an eye examination would occur annually. Resource use and unit costs for these exams were included in the medical maintenance costs of Advair 250/50 (Table 7.8).[19]

Table 7.8 Additional Costs for Maintenance Treatment – Advair 250/50

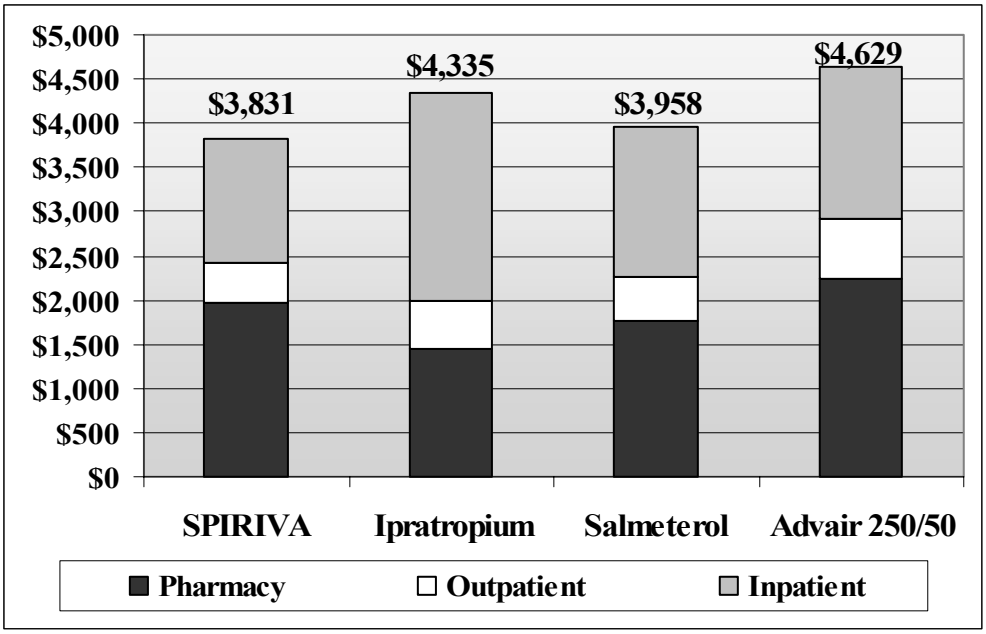
	All COPD Disease States: Advair 250/50 Maintenance		
	% of Patients	Resource Use per Patient	Unit Cost
DEXA Scan (CPT 76075)	100.0%	1	$137.78
Eye Examination (CPT 92012)	100.0%	1	$63.47

- Since Advair 250/50 is a combination product containing an inhaled steroid, costs associated with separate inhaled steroid use were excluded from the Advair 250/50 treatment arm.

- Advair 250/50 cost is based on 2004 AWP of $5.45 per day.[21]

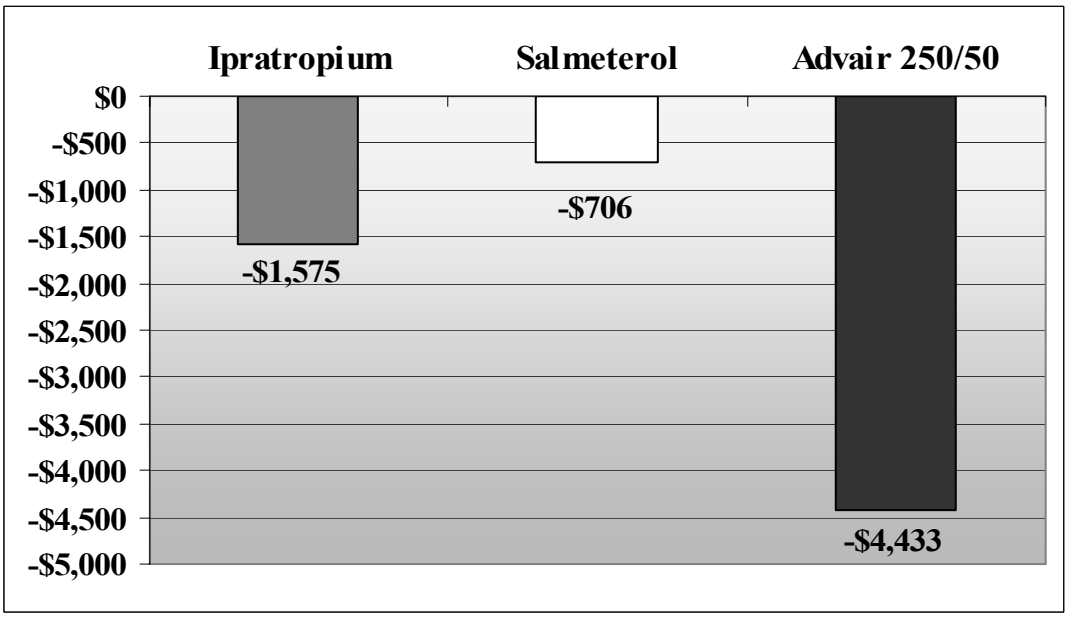
By incorporating Advair 250/50 into the cost-effectiveness model, assuming equivalent efficacy to salmeterol, accounting for the additional maintenance costs related to safety monitoring, and removing any cost inputs related to inhaled steroids, Advair 250/50 was determined to have a cost per patient per year of $4,629 (Figure 7.5). Thus, use of Advair 250/50 results in an incremental cost of $798 per patient per year when compared with SPIRIVA.

Figure 7.5 Cost per Patient per Year, by Cost Component ($US)



Furthermore, an estimate of the *cost per exacerbation avoided* with SPIRIVA was -$4,433 when compared with Advair 250/50 (Figure 7.6). As demonstrated with ipratropium and salmeterol, this negative incremental cost-effectiveness ratio indicates that SPIRIVA is less costly and more effective than Advair 250/50 (*i.e.,* dominant).

Figure 7.6 Cost per Exacerbation Avoided – inclusion of Advair 250/50 relative to SPIRIVA ($US)



7.5.3 SENSITIVITY ANALYSES

Sensitivity analyses (SA) were performed on key assumptions to test the robustness of the cost-effectiveness estimations in the model. Treatment of exacerbations is an important cost component of COPD management. Therefore, the impact of a 50% increase and 50% decrease in the inpatient hospitalization costs, and emergency room visit costs on the reduction of total direct costs with SPIRIVA were estimated:

SA1: 50% decrease in inpatient hospitalization costs
SA2: 50% increase in inpatient hospitalization costs
SA3: 50% decrease in emergency room visit cost
SA4: 50% increase in emergency room visit cost

Disease severity states are known to have an influence on the frequency of exacerbations. As a result, the impact of systematic changes in the baseline disease severity distribution of the COPD population on the reduction of total direct costs with SPIRIVA was also estimated:

SA5: Moderate/Severe/Very Severe in a ratio of 50:25:25
SA6: Moderate/Severe/Very Severe in a ratio of 25:25:50

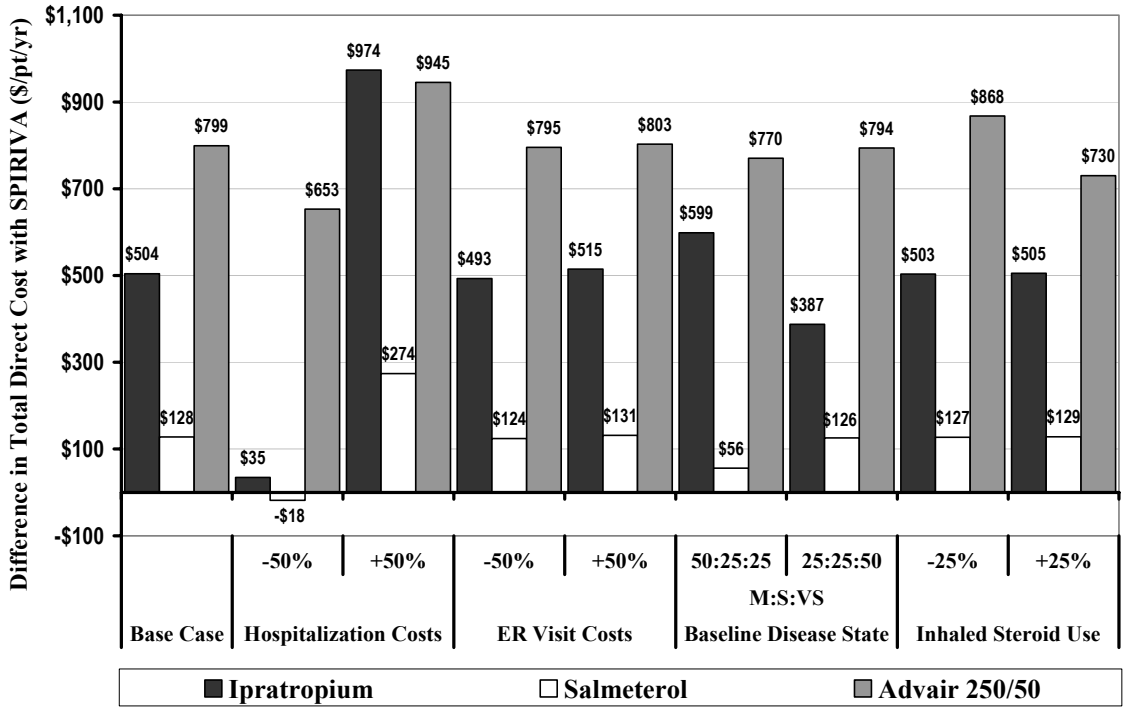
Finally, inhaled steroid use that was observed in the clinical trials may not accurately reflect current treatment patterns. Therefore, a 25% increase and 25% decrease in the proportions of patients receiving inhaled steroids in the SPIRIVA, ipratropium and salmeterol groups were also tested.

SA7: 25% decrease in inhaled steroid use
SA8: 25% increase in inhaled steroid use

Figure 7.7 presents results of the sensitivity analysis, reported as the difference in total direct costs with SPIRIVA. The results demonstrate that use of SPIRIVA results in savings in total direct costs compared with ipratropium and Advair 250/50 in all scenarios. In addition, SPIRIVA remains cost-saving compared to salmeterol in most scenarios, with the exception of a scenario where hospitalization costs are reduced by 50%, in which case use of SPIRIVA is associated with an incremental cost of $18 per patient per year compared with salmeterol.

Overall, the sensitivity analyses demonstrate that the key cost driver in the cost-effectiveness analysis is inpatient hospitalizations related to exacerbations of COPD, and that the findings of the base-case analysis are robust with respect to changes in key variables.

Figure 7.7 Sensitivity Analyses: Differences in Total Direct Costs with SPIRIVA ($/pt/year)



7.6 BUDGET IMPACT ANALYSES

7.6.1 RESULTS OF THE BUDGET IMPACT ANALYSIS

The annual total treatment cost estimates from the SPIRIVA cost-effectiveness model were used to conduct the budget impact analysis of SPIRIVA. The budget impact analysis evaluated the use of SPIRIVA as a maintenance treatment option for COPD by estimating the total budgetary impact with and without SPIRIVA.

The model is based on the following assumptions:

- Total direct annual per patient costs from the cost-effectiveness model are used to estimate the total budget impact, incorporating health resource use and effectiveness for each treatment pathway.

- This budget impact analysis includes all relevant COPD treatments, including other anticholinergics, long-acting beta$_2$-agonists (LABA) and Advair. Therefore, Combivent is included in the overall market projections for other anticholinergics. Using a daily cost of $2.62 AWP for Combivent, a weighted cost was calculated for the other anticholinergics. Based on an average ratio of 27% for ipratropium

and 73% for Combivent in market projections for each year, a drug cost per year of $944 was used in the model for other anticholinergics.[21]

- The three-year budgetary impact projections are estimated for a population of 1,000 COPD patients, with an assumed annual 3% increase of the target population.

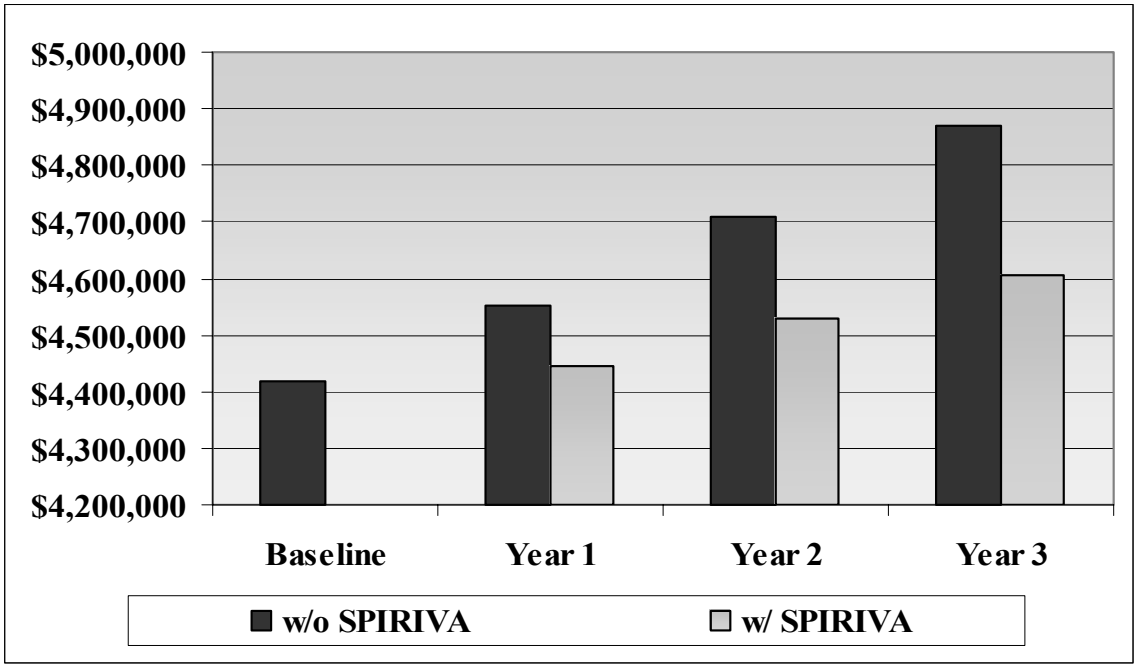
Projected changes in COPD-related market share were estimated for SPIRIVA, other anticholinergics, LABAs and Advair over a three-year period. Note that in the context of this analysis, these market share projections are relative to each other and are not meant to reflect actual market share for these products in the COPD marketplace. Projections for a scenario "without SPIRIVA" and a scenario "with SPIRIVA" are shown in Table 7.9. These market projections are based on current trends in product utilization and projections of SPIRIVA uptake in the marketplace. Note that in the scenario "With SPIRIVA", the relative market shares of the existing products are impacted not only by changes in product utilization, but also simply due to the addition of a new medication to the marketplace.

Table 7.9 Market Projections for Total Budget Impact Model

Without SPIRIVA	Year 1	Year 2	Year 3
SPIRIVA	0%	0%	0%
Other Anticholinergics	55%	53%	53%
LABA	10%	8%	5%
Advair	35%	39%	42%
With SPIRIVA	Year 1	Year 2	Year 3
SPIRIVA	20%	29%	40%
Other Anticholinergics	39%	34%	26%
LABA	8%	6%	4%
Advair	33%	31%	30%

The results of the total budget impact analysis demonstrate a net cost savings in total budget associated with the use of SPIRIVA (Figure 7.8).

Figure 7.8 Projected Total Budget Impact Over 3 Years With and Without SPIRIVA ($US)



	Baseline (n=1,000)	Year 1 (n=1,030)	Year 2 (n=1,061)	Year 3 (n=1,093)
Without SPIRIVA	$4,418,627	$4,550,747	$4,707,741	$4,871,744
With SPIRIVA		$4,443,163	$4,528,972	$4,607,096
Difference (Cost Savings)		-$107,584	-$178,769	-$264,648

Based on the budget impact analysis of 1,000 COPD patients, the use of SPIRIVA results in a total budget savings of $107,584 in the first year. These saving are increased to $178,769 in the second year. At year three, total budget savings with SPIRIVA are $264,648. This results in a cumulative total budget savings of approximately $551,000 over three years. The results of this budget impact analysis demonstrate that use of SPIRIVA as a maintenance treatment option for COPD patients can result in cost savings in the total health care budget. Table 7.10 presents the projected medical and pharmacy budget impacts with the use of SPIRIVA.

Table 7.10 Projected Medical and Pharmacy Budget Impacts Over 3 Years With and Without SPIRIVA ($US)

Medical Budget Impact

	Baseline (n=1,000)	Year 1 (n=1,030)	Year 2 (n=1,061)	Year 3 (n=1,093)
Without SPIRIVA	$2,647,762	$2,726,784	$2,802,648	$2,893,518
With SPIRIVA		$2,538,775	$2,542,068	$2,515,245
Difference (Cost Savings)		-$188,009	-$260,580	-$378,273

Pharmacy Budget Impact

	Baseline (n=1,000)	Year 1 (n=1,030)	Year 2 (n=1,061)	Year 3 (n=1,093)
Without SPIRIVA	$1,770,866	$1,823,963	$1,905,094	$1,978,227
With SPIRIVA		$1,904,388	$1,986,904	$2,091,849
Difference (Incremental Cost)		$80,425	$81,810	$113,622

Use of SPIRIVA results in an incremental pharmacy cost of approximately $78 per patient per year in the first year and increases to $104 per patient per year at year three. However, these costs are completely offset by savings in medical costs, resulting in a net total budget savings.

7.6.2 SENSITIVITY ANALYSIS – TOTAL BUDGET IMPACT

The robustness of the budget impact analysis was tested in sensitivity analyses using the same parameters described in Section 7.6.3. Figure 7.9 presents a tornado diagram of the results of the sensitivity analyses, in terms of difference in total budget impact in the first year. Figure 7.10 presents the sensitivity analyses based on the difference in cumulative total budget impact after 3 years. These results demonstrate that the use of SPIRIVA results in a net cost savings in all scenarios, with the key cost driver being inpatient hospitalizations.

Figure 7.9 Sensitivity Analysis: Total Budget Impact at Year 1

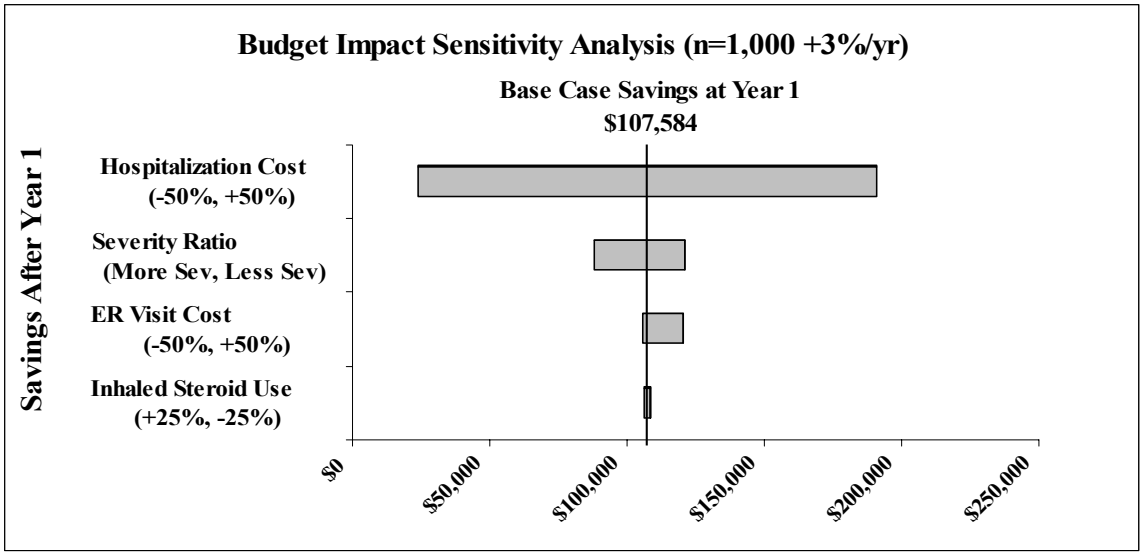
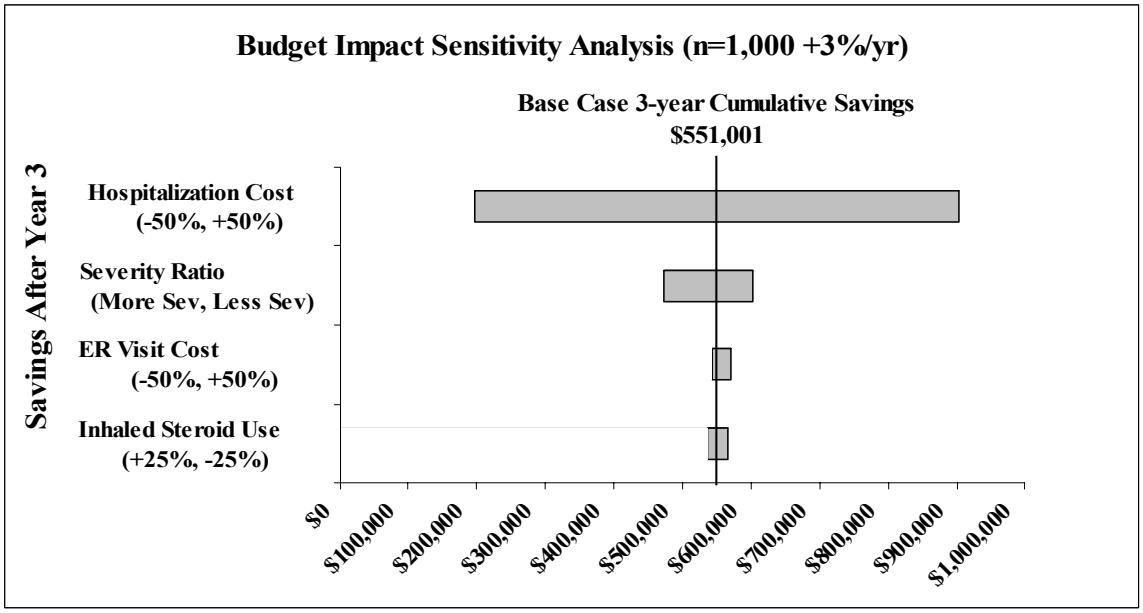


Figure 7.10 Sensitivity Analysis: Cumulative Total Budget Impact after Year 3



7.7 CONCLUSIONS: THE ECONOMIC VALUE OF SPIRIVA

The information presented in the model supports the cost-effectiveness of SPIRIVA in the maintenance treatment of COPD compared with the active comparators ipratropium and salmeterol. Use of SPIRIVA resulted in cost savings relative to ipratropium, salmeterol and Advair 250/50, with differences in total annual costs per patient ranging from -$127 with salmeterol to -$798 with Advair 250/50. The results of the cost-effectiveness analyses indicate that SPIRIVA is dominant, (*i.e.,* more effective and less

costly) compared with ipratropium, salmeterol and Advair 250/50. These results are robust with respect to changes in key variables.

The budget impact analysis demonstrates that the use of SPIRIVA will result in total budget savings of $107,584 in the first year, with cumulative total budget savings of $551,000 for an initial cohort of 1,000 COPD patients after three years. Incremental pharmacy expenditures are completely offset by decreased medical expenditures.

In conclusion, these pharmacoeconomic evaluations demonstrate that SPIRIVA is less costly and more effective than ipratropium, salmeterol and Advair 250/50. Use of SPIRIVA in the maintenance treatment of COPD is cost-effective and generates cost savings in the total health care budget for managed care organizations.

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ASSESSMENT MODALITIES USED IN CLINICAL TRIALS

This appendix provides a brief description of the key assessment measures used in clinical trials conducted in support of SPIRIVA.

A-1.1 LUNG FUNCTION MEASURES

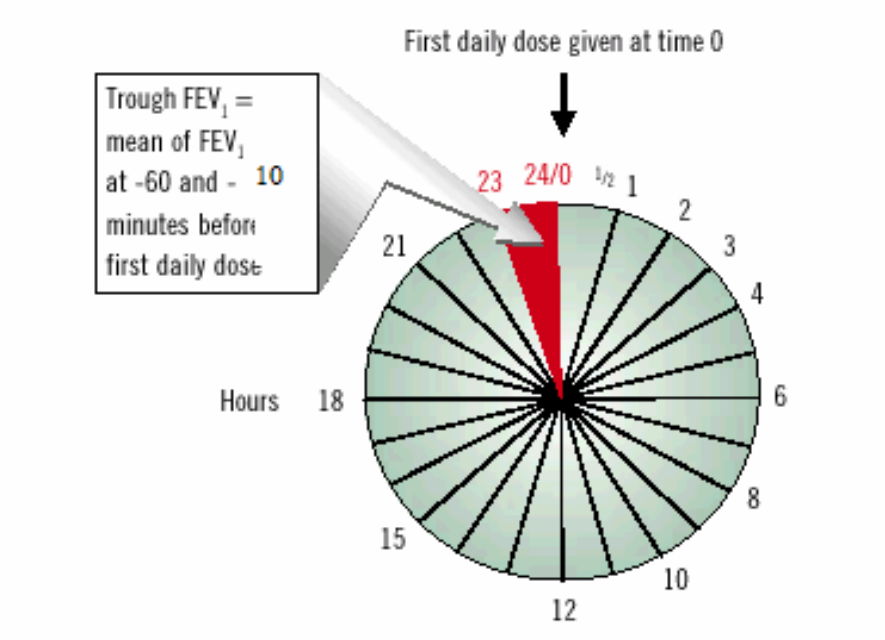
a. Spirometry

In clinical trials, primary measures of lung function were two assessments of forced expiration from the lung: forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)—spirometric assessments that can be used to identify patients with chronic obstructive pulmonary disease (COPD) and assess the level of severity of the disorder.[1]

FEV_1 provides a reliable measure of airflow obstruction.[2] FEV_1 is reduced in patients with COPD, due to an increase in airway resistance and a reduction in the elastic recoil of the lung.[3] FVC gives indirect information on lung hyperinflation; when patients experience hyperinflation, expiration ends prematurely despite abnormally large total lung capacity (TLC), so that FVC is reduced.[3] The ratio of FEV_1 to FVC may be used to differentiate between restrictive lung disease (e.g., pulmonary fibrosis) and obstructive lung disease (e.g., COPD).[3]

In the pivotal 1-year and 6-month clinical trials, trough FEV_1 was a primary efficacy endpoint.[4] Trough FEV_1 was defined as the mean of two FEV_1 readings taken at 60 minutes and 5 minutes before the first daily dose of study drug (i.e., at the end of the dosing interval —about 23 to 24 hours postdose for once-daily SPIRIVA).[4] Figure A-1.1 depicts trough measurement.

Figure A-1.1: Trough FEV_1 Measurement



The mean average FEV_1 was the average response during the 3-hour postdose period. The mean peak FEV_1 was the peak response following drug administration.[4]

b. Peak expiratory flow rate

Spirometric findings of efficacy were confirmed by daily at-home measurements of peak expiratory flow rate (PEFR), conducted by patients in the morning and the evening. Weekly means were computed from these data.[4] In one pivotal clinical trial (1-year, SPIRIVA vs. placebo), PEFR was assessed via the AirWatch™ Monitor (Enact Health Management Systems, Mountain View, California, USA); in other pivotal trials, PEFR was measured by manual peak flow meter and recorded in patient diaries.[4,5]

A-1.2 DYSPNEA

Dyspnea (shortness of breath) is the reason most people with COPD seek medical attention.[6] The Baseline Dyspnea Index (BDI) and the Transition Dyspnea Index (TDI)—have been developed to improve clinical measurement of dyspnea.[7] Clinical studies with SPIRIVA used these instruments.[4]

BDI measures dyspnea at baseline in three domains: functional impairment, magnitude of task, and magnitude of effort. Functional impairment determines the impact of breathlessness on the person's ability to carry out activities. Magnitude of task

determines the type of task that causes breathlessness. Magnitude of effort establishes the level of effort that results in breathlessness.[8] Each domain is graded from 0 (very severe impairment) to 4 (no impairment)[8] based on patients' responses to clinical interviews,[7] and the values are added for a combined focal score consisting of the sum of each domain (0 to 12).[4,7,8] Subsequently, TDI is used to denote changes from BDI determined at baseline[7] —for example, as a result of treatment. TDI measures changes in the 3 domains, with scores ranging from –3 (major deterioration) to +3 (major improvement).[7,8] The TDI focal score consists of the sum of each domain (–9 to +9).[7,8] A change of at least one unit in TDI is considered a minimal important meaningful difference, and this standard was used in trials with SPIRIVA.[4]

In addition, for the SPIRIVA exercise trial, the Borg scale was also used to rate dyspnea. This scale rates perceived exertion in response to exercise intensity (i.e., during stationary cycling or treadmill walking) during work on a cycle ergometer.[9] Scale values range from 0 to 10 (lightest to hardest perceived exertion).[9]

A-1.3 EXACERBATIONS AND HOSPITALIZATIONS

Clinical trials for SPIRIVA assessed exacerbations of COPD and related hospitalizations, since prevention of these events is key to both patient care and cost reduction.[10-15] In the core clinical trials, an exacerbation was defined as a complex of two or more respiratory symptoms(increased or new onset) including increased dyspnea, sputum production, purulence and cough, reported as adverse events with a duration of ≥3 days; the hospitalizations assessed were those associated with a COPD exacerbation.[4] In the subsequent trial specifically designed to prospectively evaluate exacerbations as a primary outcome measure, an exacerbation was similarly defined by a complex of respiratory symptoms with a duration of at least 3 days, and requiring treatment with antibiotics, steroids or hospitalization.

A-1.4 HEALTH-RELATED QUALITY OF LIFE (HRQOL)

One of the most important aims of COPD treatment is to enhance HRQoL, which can be impaired due to loss of lung function and reduced exercise capacity.[16,17] When evaluating HRQoL, it is accepted that a disease-specific questionnaire, when available, is preferable to a generic HRQoL tool.[17] For that reason, in clinical trials with SPIRIVA, the St. George's Respiratory Questionnaire (SGRQ) was used to evaluate HRQOL specifically related to COPD.[4]

The SGRQ is a validated patient-administered questionnaire that contains 76 items,[16] divided into 3 sections:

- *Symptoms*: This section includes questions about such symptoms as cough or breathlessness. Answers to questions in this section are multiple choice, with options over a range of symptom frequencies from "none" to "every day."[16]

- *Activity*: This section asks about activities of daily living that either cause or become limited by dyspnea. Patients give yes or no answers.[16]

- *Impacts*: This section assesses the effect of respiratory problems on psychosocial factors, such as employment or social stigmatization; yes or no responses are elicited as well.[16]

Each section of the SGRQ is scored separately on a scale of 0% to 100%, with 0% indicating no impairment in life quality; calculation from raw score to scale score uses weights assigned to each item in the questionnaire. A total score is also derived, using the 0% to 100% scale.[16]

A change (decrease) of ≥4 scoring units in the total score constitutes a clinically meaningful improvement in SGRQ.[18] Examples of changes required for an improvement of 4 units on the SGRQ include[18]:

- "No longer has to walk more slowly than other people, no longer breathless on getting washed or dressed or on bending over."

- "No longer takes a long time to wash or dress, can now walk up stairs without stopping and go out for entertainment."

A-1.5 ADDITIONAL MEASURES

In the exercise trial for SPIRIVA, numerous additional measures of lung hyperinflation and exercise capacity were used.

The trial used body plethysmography to determine functional residual capacity (FRC), total lung capacity (TLC), and residual volume (RV). Inspiratory capacity (IC) was calculated as TLC minus FRC.[19] In body plethysmography, the patient is enclosed in a special chamber equipped to measure pulmonary pressure, flow, or volume changes.[20] The technique is especially suited to showing lung hyperinflation (as evidenced by increased FRC and TLC) and air-trapping (as indicated by increased RV).[21]

The trial conducted exercise testing via cycle ergometry,[19] a common method of providing controlled exercise.[3] Exercise endurance time was assessed during constant work rate exercise at 75% maximum work rate (based on incremental exercise testing) via cycle ergometry.[19]

A-1.6 ASSESSMENT FLOW CHARTS

The following charts show the scheduled assessment measures for the 3 pairs of pivotal clinical trials:

Table A-1.1 Assessment Flow, 1-Year Trial: SPIRIVA vs. Placebo [22,23]

Week	-2	0	1	4	7	10	13	19	25	31	37	43	49‡	52
Visit	1 Screen	2 Random	3	4	5	6	7	8	9	10	11	12	13 Stop	14 Follow-up
PFT*		X	X		X		X		X		X		X	
BDI		X												
TDI					X		X		X		X		X	X
SGRQ		X			X		X		X		X		X	X
AEs†	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab	X						X		X		X		X	

* In addition to spirometry, AM and PM (i.e., upon arising and at bedtime) peak expiratory flow rates (PEFRs) were measured at home by patients using the AirWatch™ Monitor (Enact Health Management Systems, Mountain View, California, USA).[5]
† Exacerbations defined under AEs: a complex of respiratory events, reported as AEs, with a duration of ≥3 days.[3]
‡ Final, complete assessment, day 344.[5]
PFT=pulmonary function testing (FEV_1, FVC); BDI=baseline dyspnea index; TDI=transition dyspnea index; SGRQ=St. George's Respiratory Questionnaire; AEs=adverse events; Lab=laboratory assessments.

Table A-1.2 Assessment Flow, 1-Year Trial: SPIRIVA vs. Ipratropium [24]

Week	-2	0	1	4	7	10	13	19	26	32	39	45	52§	55
Visit	1 Screen	2 Random	3‡	4	5	6	7	8	9	10	11	12	13 Stop	14 Follow-up
PFT*		X	X		X		X		X		X		X	
BDI		X												
TDI			X		X		X		X		X		X	X
SGRQ		X	X		X		X		X		X		X	X
AEs†								X	X	X	X	X	X	X
Lab	X						X		X		X		X	

* In addition to spirometry, AM and PM PEFRs were measured at home.[24]
† Exacerbations defined under AEs: a complex of respiratory events, reported as AEs, with a duration of ≥3 days.[4]
‡ Differs from SPIRIVA vs. placebo 1-year study, in that TDI was assessed at week 1 (day 8).
§ Final, complete assessment, day 364.[24]
PFT=pulmonary function testing (FEV_1, FVC); BDI=baseline dyspnea index; TDI=transition dyspnea index; SGRQ=St. George's Respiratory Questionnaire; AEs=adverse events; Lab=laboratory assessments.

Table A-1.3 Assessment Flow, 6-Month Trial: SPIRIVA vs. Salmeterol vs. Placebo [25]

Week	-2	0	2	4	8	12	16	20	24	27
Visit	1 Screen	2 Random	3	4	5	6	7	8	9 Stop	10 Follow -up
PFT*		X	X		X		X		X	
BDI		X								
TDI					X		X		X	X
SGRQ		X			X		X		X	X
AEs†		X	X	X	X	X	X	X	X	X
Lab	X								X	

***** In addition to spirometry, AM and PM PEFRs were measured at home.[4]
† Exacerbations defined under AEs: a complex of respiratory events, reported as AEs, with a duration of ≥3 days.[4]
PFT=pulmonary function testing (FEV_1, FVC); BDI=baseline dyspnea index; TDI=transition dyspnea index; SGRQ=St. George's Respiratory Questionnaire; AEs=adverse events; Lab=laboratory assessments.

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GLOSSARY OF TERMS

Alveolar volume: Volume of air that can be contained in the alveoli, measured by single-breath inert gas dilution.

Alveoli (singular, alveolus): The final, small branches of the lung, located in peripheral lung regions and responsible for blood-lung gas exchange.

Baseline Dyspnea Index (BDI): Measurement of dyspnea at baseline in three domains: functional impairment, magnitude of task, and magnitude of effort; BDI also generates baseline focal scores, which represent total score of the 3 domains.

Body plethysmography: Technique in which a patient is enclosed in a special chamber that can measure pulmonary pressure, flow, or volume changes.

Borg Dyspnea Scale: Scale that rates perceived breathlessness in response to an exercise load.

Bronchoconstriction: Narrowing of the lumina of the airways.

Bronchodilator: An agent that relaxes bronchial smooth muscle, thereby creating dilation of the airways.

Chronic bronchitis: An inflammation of the bronchi, which persists or recurs repeatedly. The condition is most commonly caused by long-term irritation of the bronchial tubes, resulting from exposure to such airborne pollutants as cigarette smoke. The disorder is defined by the presence of cough productive of sputum on most days for at least 3 months for at least 2 consecutive years.

Chronic obstructive pulmonary disease (COPD): A disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases. Pathologically, COPD is characterized by a combination of small airway disease (i.e., obstructive bronchiolitis, or chronic bronchitis) and parenchymal destruction (i.e., emphysema).

Dyspnea: Breathlessness or difficulty breathing that can include the feeling of not getting enough air.

Emphysema: A lung disease characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. There is progressive damage of the alveoli and surrounding supportive tissue, causing air to become trapped in the lungs. In advanced disease, large air cysts develop where normal lung tissue used to be. Cigarette smoking, tobacco smoke,

and other pollutants can cause emphysema. Symptoms include shortness of breath, chronic cough, and wheezing.

Endurance time (ET): The amount of time a patient can exercise before the onset of COPD symptoms.

European Community for Coal and Steel (ECCS): Organization that has developed regression equations to determine predicted normal FEV_1.

Exacerbations (in COPD): Periods of worsening of symptoms, beyond usual day to day fluctuations, including increases in dyspnea, cough, sputum production and purulence.

Forced expiratory volume in 1 second (FEV_1): The amount of air a patient can forcibly exhale in 1 second. A normal FEV_1 can be calculated based a patient's height, age and gender. FEV_1 can be reported as percent of predicted normal. In SPIRIVA trials, the predicted normal FEV_1 was determined by either the Morris Equation or by European Community for Coal and Steel (ECCS) regression equations.

Forced vital capacity (FVC): The total volume of air a patient can forcibly exhale from the point of maximum inspiration to the end of expiration.

Functional residual capacity (FRC): The volume of air in the lungs at the end of a resting (or tidal) breath.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): Formed in collaboration with the US National Heart, Lung, and Blood Institute and the World Health Organization. Among the objectives of GOLD are to increase awareness of COPD and to help lessen the morbidity and mortality associated with the disease.

HandiHaler®: A reusable, breath-actuated, single-dose, dry-powder inhalation device developed especially for use with SPIRIVA capsules.

Health-related quality of life (HRQoL): The impact of health on the quality of an individual's life. COPD specific assessment tools include the St. George's Respiratory Questionnaire (SGRQ).

Hyperinflation: A result of COPD, in which patients have abnormally large lung volumes due to air trapping. Hyperinflation results in breathlessness and premature termination of physical activities.

Inspiratory capacity (IC): A lung volume determined by subtracting the functional residual capacity (FRC) from the total lung capacity (TLC). It is the volume from the end of a resting breath to a maximum inspiration.

Inspiratory flow rate: The flow rate (volume per unit time) at which a patient inhales air into the lungs.

Maximal work capacity (W_{cap}): The highest workload attained during formal exercise testing.

Maximum recommended human daily dose (MRHD): The highest dose of a medication that a person can safely consume on a daily basis.

Metered dose inhaler (MDI): A device that delivers a specific amount of medication in aerosol form inhaled through the mouth down into the lungs.

Muscarinic receptors: Cholinergic (i.e., cell-surface receptors that bind acetylcholine) receptors. Three subtypes (M_1, M_2, and M_3) are responsible for bronchoconstriction and have been identified in the human airway and lung. Five subtypes have been identified based on molecular structure (M_1 to M_5).

Pack-years: A measure of how heavily a person has smoked cigarettes. Pack-years are calculated by multiplying the number of years a person has smoked times the average number of cigarettes he or she smoked per day, divided by 20 (the number of cigarettes in a pack).

Parenchymal: Pertaining to the functional elements of an organ. COPD is characterized by parenchymal destruction, or emphysema.

Residual volume (RV): The volume of air remaining in the lungs after maximum exhalation.

Peak expiratory flow rate (PEFR): The maximum flow of air during forced expiration.

Single-breath inert gas dilution: Test in which a patient inhales an inert gas (such as helium) from a closed container of a known volume; data from the test can be used to calculate lung volumes.

St. George's Respiratory Questionnaire (SGRQ): A self-completed questionnaire containing 76 items that assess health-related quality of life (HRQoL) based on symptoms (such as dyspnea), activity levels, and psychosocial impacts of lung disease. The SGRQ also generates a total life-quality score.

Tachyphylaxis: Diminished response to repeated use of medication.

Total lung capacity (TLC): The total volume of air in the lungs.

Transition Dyspnea Index (TDI): Measure of changes in dyspnea from the Baseline Dyspnea Index (BDI). TDI examines change (improvement or deterioration) in three domains established by BDI: functional impairment, magnitude of task, and magnitude of effort. A focal score is also generated, which is a total of scores for the three domains.

SPIRIVA THERAPY COST MODEL TECHNICAL DOCUMENT

1. Introduction

Boehringer Ingelheim has conducted a series of Phase III clinical trials to assess the effectiveness and costs of SPIRIVA. Two one-year usual care-controlled trials with an identical design were conducted in the United States. In these trials SPIRIVA was compared to placebo (usual care), where concomitant use of theophylline, inhaled steroids, minimal doses of oral corticosteroids (equivalent to ≤10 mg prednisone/day), and concomitant use of PRN albuterol MDI was allowed throughout the study period. Long-acting $Beta_2$-agonists (eg, salmeterol or formoterol) were not permitted.

Two one-year ipratropium-controlled trials with an identical design were conducted in the Netherlands and Belgium. Finally, two three-arm trials were conducted to compare SPIRIVA to salmeterol and placebo. The latter trials were conducted in a total of 17 countries and patients were followed for 6 months.

Using the data from the clinical trials Oostenbrink and colleagues developed the Markov Model and populated the same with utilization and costs from the Netherlands[1-2]. We took the basics of the model and adapted it for the US Market using US resource utilizations and costs. The methodology for this is explained in Chapter 7 of the AMCP Value dossier[3]. This Technical document discusses the conversion of the Markov model for incorporation into the Therapy Cost model, population of the Therapy Cost model with various model parameters and generation of the Cost Effectiveness Ratios and the Budget Impact.

2. Aim

The aim of the Therapy Cost Model was to replicate the one-year Markov Model by estimating the costs and effects of SPIRIVA compared to all its relevant alternatives. The model is primarily driven by disease-severity states and exacerbations and is structured so that any health plan can customize the data to their particular patient and resources use/cost characteristics.

3. Therapy Cost Model

Therapy Cost GPS is a pharmacoeconomic modelling tool developed by Pfizer and has been used to successfully model several disease states and therapies. Based on a Visual Basic interface the Therapy Cost program conducts Budget Impact as well as Cost Effectiveness Analysis in the same model. A Markov process can also be model within Therapy Costs with minor modifications. A Markov process is based on the idea that patients are always in a certain disease state and that they can change between disease states once during each cycle. Patients also have a certain probability to experience events, depending on the disease state they are in. Because of the above features, a Markov process is well suited to model a chronic disease like COPD, where patients can be classified into disease severity states with relative ease, and where patients run a continuous risk of experiencing an exacerbation. The Markov model was modified for purposes of entry into Therapy Cost. A linear estimation of the Markov process was used. The transition probabilities for each drug are presented in the Excel sheet (SpirivaTCModelNotes2.xls) accompanying the model.

Therapy Cost is specified by first defining the cycle; then the therapies; followed by the population; the various resources as cost parameters (global event, global recurring, local

event and local recurring); setting up percent receiving resources and units per cycle; setting up of the timelines and finally the market share distributions.

A. Cycle Definition

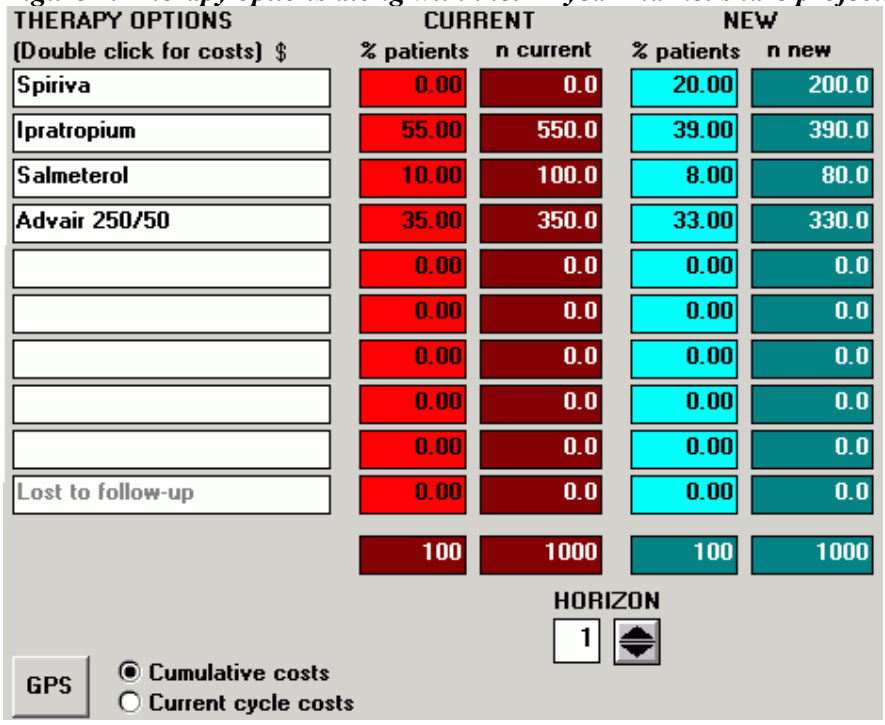
The length of the Markov cycle was chosen so that the probability of experiencing more than one exacerbation during the same cycle is minimized. In this model a Markov cycle with duration of 1 month. However, the first cycle had duration of 8 days. This is because an initial improvement in pulmonary function within the first 8 days after the start of SPIRIVA that remained constant thereafter. In Therapy Cost the transition probabilities were adjusted using an Excel model to account for the first 8 days and hence only 1-month cycles were used.

B. Therapy Options

Four treatment alternatives will be compared in the model:

1. SPIRIVA —18 mcg inhalation administered once-daily via the HandiHaler® device.
2. Ipratropium—2 puffs of 20 mcg administered four times daily via a metered dose inhaler.
3. Salmeterol—2 puffs of 25 mcg inhalation administered twice-daily via a metered dose inhaler.
4. Advair 250/50.

Figure 1. Therapy options along with their 1-year market share projections



C. Patient Population (Disease States)

A population of 1000 COPD patients was distributed according to the Figure 2 below into the various Disease States modelled.

Figure 2:

		CYCLE START				CYCLE END
Inc.	Member group	n members	% w disease	Per cycle growth % or Per cycle decline %		n members
☒ #1	Moderate	250	100			250.0
☒ #2	Severe	500	100			500.0
☒ #3	Very Severe	250	100			250.0

D. Costs

The Therapy Cost model classifies resource use and costs into either global (applicable to all therapies) or local (applicable to the particular therapy) and into either event (occurring once) or recurring. Thus we have 4 types of resources Global Event, Global Recurring, Local Event and Local Recurring. For this model were modelled as Global Recurring Costs except for the cost of the primary therapies which were modelled as Local Recurring Costs. Refer to Chapter 7. AMCP Dossier for a detailed discussion on the selection and costing of the resources. Example screen captures of these costs are provided below.

Figure 3. Global Recurring Costs

ON/OFF	Service descriptor	Cost/unit	ON/OFF	Service descriptor	Cost/unit
☒	Maint. OPt visit GP	$ 52.65	☒	NSE Systemic Steroids	$ 0.13
☒	Maint. Spirometry	$ 32.48	☐		$ 0.00
☒	Maint. FLu vaccine	$ 31.87	☐		$ 0.00
☒	Maint. B-adrenergics	$ 0.60	☐	Non Sev Exacerb	$ 0.00
☒	Maint. Theophylline	$ 0.74	☒	SE ICU day	$ 1914.23
☒	Maint. Inhaled Steroids	$ 2.32	☒	SE non-ICU stay	$ 1383.44
☒	Maint. OPt visit Pulm.	$ 82.14	☒	SE Emergency Room	$ 654.97
☒	Maint. DEXA [Advair only]	$ 137.78	☒	SE OPt visit Pulmonologist	$ 119.11
☒	Maint. Eye exam [Advair only	$ 63.47	☒	SE OPt Visit GP	$ 82.14
☐	Maintenance	$ 0.00	☒	SE Other Pract. visits	$ 21.28
☒	NSE non-ICU	$ 1383.44	☒	SE Antibiotics	$ 5.05
☒	NSE Emergency Room	$ 654.97	☐		$ 0.00
☒	NSE OPt visit Pulmnologist	$ 119.11	☒	SE Systemic Steroids	$ 0.13
☒	NSE OPt visit GP	$ 82.14	☐		$ 0.00
☒	NSE Other Pract. visits	$ 21.28	☐		$ 0.00
☒	NSE Antibiotics	$ 5.05	☐		$ 0.00
☐		$ 0.00	☐	Sev Exacerb	$ 0.00

Figure 4. Local recurring costs for primary drug therapies

E. Percent Receiving Resources and Units Per Cycle

After setting up the Global Recurring costs, we still need to specify percent of population that received the resources and the units per cycle that were consumed. To determine this we need the transition probabilities of moving from one disease state to another as well as the probability of exacerbations (severe and non-severe). These transition and exacerbation probabilities differed based on treatment. The conversion of the probabilities to Therapy cost input probabilities (linear estimation of the Markov) is conducted using the excel spreadsheet and screen captures for SPIRIVA are shown here for demonstration purposes.

Figure 5. Tab Tio(tropium) from Excel Spreadsheet shows Computation of End State Probabilities that were used to derive the TC model.

Baseline Distribution

Moderate	Severe	Very Severe
0.25	0.5	0.25

Transition probabilities

			First cycle (8 days) TO			Subsequent cycles (per month) TO		
			Moderate	Severe	Very Severe	Moderate	Severe	Very Severe
Spiriva	FROM	Moderate	0.907	0.092	0.001	0.957	0.04	0.003
		Severe	0.259	0.716	0.025	0.023	0.954	0.023
		Very Severe	0.01	0.341	0.649	0.001	0.045	0.954

Time point	Probabilities		
	Moderate	Severe	Very Severe
0	0.25	0.5	0.25
8 days	0.35875	0.46625	0.175
1 month	0.354223	0.467028	0.17875
2 month	0.349911	0.467757	0.182332
3 month	0.345806	0.468441	0.185753
4 month	0.341896	0.469084	0.18902
5 month	0.338173	0.469688	0.192139
6 month	0.334626	0.470256	0.195118
7 month	0.331248	0.470789	0.197963
8 month	0.328031	0.471291	0.200678
9 month	0.324966	0.471764	0.203271
10 month	0.322046	0.472208	0.205746
11 month	0.319265	0.472627	0.208108
12 month	0.316615	0.473022	0.210364
p	**0.329682**	**0.472157**	**0.19816**

Severe Exacerbations	Probabilities		
	Moderate	Severe	Very Severe
	0.1048	0.1421	0.1898
8 days	0.000516	0.001337	0.000939
1 month	0.001428	0.003757	0.002691
2 month	0.001914	0.005105	0.003724
3 month	0.001892	0.005112	0.003794
4 month	0.00187	0.005119	0.00386
5 month	0.00185	0.005126	0.003924
6 month	0.001831	0.005132	0.003985
7 month	0.001812	0.005138	0.004043
8 month	0.001795	0.005143	0.004098
9 month	0.001778	0.005148	0.004151
10 month	0.001762	0.005153	0.004202
11 month	0.001747	0.005158	0.00425
12 month	0.001732	0.005162	0.004296
Cumulative p	**0.021926**	**0.061592**	**0.047957**

Nonsevere Exacerbations	Probabilities		
	Moderate	Severe	Very Severe
0	0.8952	0.8579	0.8102
8 days	0.004406	0.008074	0.00401
1 month	0.012202	0.022683	0.011487
2 month	0.016351	0.030819	0.015895
3 month	0.016159	0.030864	0.016193
4 month	0.015977	0.030906	0.016478
5 month	0.015803	0.030946	0.01675
6 month	0.015637	0.030984	0.01701
7 month	0.015479	0.031019	0.017258
8 month	0.015329	0.031052	0.017495
9 month	0.015185	0.031083	0.017721
10 month	0.015049	0.031112	0.017936
11 month	0.014919	0.03114	0.018142
12 month	0.014795	0.031166	0.018339
Cumulative p	**0.187291**	**0.371848**	**0.204715**

The highlighted probabilities were then used to modify the percent of population using the resources. The reason being that the initial probability of being in a disease state was fixed however, due to transitions over a year, the year-end probability was different. Thus we took an average of the maintenance probability over all the cycles. In some cases this average was greater than the initial probability and in some cases it was lower. If the percent of patients receiving resource was 100% and the average probability of being in that state and the year-end was greater (e.g. = 0.3296) than the initial probability (0.25), then the percent of patients receiving the service was adjusted up (131.87%). This is shown in Columns 1 and 2 in Figure 6 below. The annual utilization of resources was adjusted to get the monthly utilization or units per cycle. The data in the second and fourth columns was then entered into Therapy Cost.

Figure 6. Tab Tio(tropium) from Excel Spreadsheet shows Computation Transition Probability Adjusted Resource Use Percentages and Units per Cycle that were used to populate the TC model.

Moderate Disease Maintenance

	Actual % Receiving Service	Transition Probability Adjusted % Receiving	Total Units	Units/Cycle
OPt visit GP	*100%*	*131.87%*	*3*	*0.25*
Spirometry	*100%*	*131.87%*	*1*	*0.08*
FLu vaccine	*100%*	*131.87%*	*1*	*0.08*
B-adrenergics	*98.40%*	*129.76%*	*290.64*	*24.22*
Theophylline	*9.40%*	*12.40%*	*320.83*	*26.74*
Inhaled Steroids	*39.60%*	*52.22%*	*285.07*	*23.76*

Moderate Disease Non Severe Exacerbation

non-ICU	*8.23%*	*6.17%*	*5.68*	*0.47*
Emerg Room	*2.87%*	*2.15%*	*1*	*0.08*
OPt visit Pulm.	*36.30%*	*27.19%*	*0.94*	*0.08*
OPt visitGP.	*45.50%*	*34.09%*	*1.45*	*0.12*
Other visits	*3.80%*	*2.85%*	*7.11*	*0.59*
Antibiotics	*71.30%*	*53.42%*	*11.13*	*0.93*
Systemic steroids	*48.40%*	*36.26%*	*15.99*	*1.33*

Moderate Disease Severe Exacerbation

ICU	*11.10%*	*0.97%*	*4.3*	*0.36*
non-ICU	*77.80%*	*6.82%*	*5.66*	*0.47*
Emerg Room	*25.00%*	*2.19%*	*1*	*0.08*
OPt visit Pulm.	*47.20%*	*4.14%*	*1.74*	*0.15*
OPt visitGP.	*44.40%*	*3.89%*	*1.58*	*0.13*
Other visits	*13.90%*	*1.22%*	*3.6*	*0.30*
Antibiotics	*75.00%*	*6.58%*	*15.67*	*1.31*
Systemic steroids	*77.80%*	*6.82%*	*30.96*	*2.58*

Severe Disease Maintenance

OPt visit GP	*70%*	*66.10%*	*4*	*0.33*
Spirometry	*100.00%*	*94.43%*	*1*	*0.08*
FLu vaccine	*100.00%*	*94.43%*	*1*	*0.08*
B-adrenergics	*97.30%*	*91.88%*	*285.78*	*23.82*
Theophylline	*15.10%*	*14.26%*	*276.38*	*23.03*
Inhaled Steroids	*42.50%*	*40.13%*	*278.33*	*23.19*
OPt visit Pulm.	*30.00%*	*28.33%*	*4*	*0.33*

Severe Disease Non Severe Exacerbation

non-ICU	*8.23%*	*6.12%*	*5.68*	*0.47*
Emerg Room	*2.87%*	*2.13%*	*1*	*0.08*
OPt visit Pulm.	*36.30%*	*27.00%*	*0.94*	*0.08*
OPt visitGP.	*45.50%*	*33.84%*	*1.45*	*0.12*
Other visits	*3.80%*	*2.83%*	*7.11*	*0.59*
Antibiotics	*71.30%*	*53.03%*	*11.13*	*0.93*
Systemic steroids	*48.40%*	*35.99%*	*15.99*	*1.33*

Severe Disease Severe Exacerbation

ICU	*11.10%*	*1.37%*	*4.3*	*0.36*
non-ICU	*77.80%*	*9.58%*	*5.66*	*0.47*
Emerg Room	*25.00%*	*3.08%*	*1*	*0.08*
OPt visit Pulm.	*47.20%*	*5.81%*	*1.74*	*0.15*
OPt visitGP.	*44.40%*	*5.47%*	*1.58*	*0.13*
Other visits	*13.90%*	*1.71%*	*3.6*	*0.30*
Antibiotics	*75.00%*	*9.24%*	*15.67*	*1.31*
Systemic steroids	*77.80%*	*9.58%*	*30.96*	*2.58*

Very Severe Disease Maintenance

OPt visit GP	*30%*	*23.78%*	*6*	*0.50*
Spirometry	*100.00%*	*79.26%*	*1*	*0.08*
FLu vaccine	*100.00%*	*79.26%*	*1*	*0.08*
B-adrenergics	*96.30%*	*76.33%*	*278.76*	*23.23*
Theophylline	*21.60%*	*17.12%*	*280.26*	*23.36*
Inhaled Steroids	*46.00%*	*36.46%*	*278.47*	*23.21*
OPt visit Pulm.	*70.00%*	*55.48%*	*6*	*0.50*

The Therapy cost input sections for Spiriva Moderate Disease is shown below in Figure 7.

Figure 7:

Service descriptor	% receiving service	Units per cycle	Service descriptor	% receiving service	Units per cycle
Maint. OPt visit GP	131.87 %	0.25	NSE Systemic Steroids	36.26 %	1.33
Maint. Spirometry	131.87 %	0.08		%	
Maint. FLu vaccine	131.87 %	0.08		%	
Maint. B-adrenergics	129.76 %	24.22	Non Sev Exacerb	%	0.00
Maint. Theophylline	12.40 %	26.74	SE ICU day	0.97 %	0.36
Maint. Inhaled Steroids	52.22 %	23.76	SE non-ICU stay	6.82 %	0.47
Maint. OPt visit Pulm.	0.00 %	0.00	SE Emergency Room	2.19 %	0.08
Maint. DEXA [Advair only]	0.00 %	0.00	SE OPt visit Pulmonologist	4.14 %	0.15
Maint. Eye exam [Advair	0.00 %	0.00	SE OPt Visit GP	3.89 %	0.13
Maintenance	%	0.00	SE Other Pract. visits	1.22 %	0.30
NSE non-ICU	6.17 %	0.47	SE Antibiotics	6.58 %	1.31
NSE Emergency Room	2.15 %	0.08		%	
NSE OPt visit Pulmnologist	27.19 %	0.08	SE Systemic Steroids	6.82 %	2.58
NSE OPt visit GP	34.09 %	0.12		%	
NSE Other Pract. visits	2.85 %	0.59		%	
NSE Antibiotics	53.42 %	0.93		%	
	%		Sev Exacerb	%	0.00

F. Market Share Distributions

Based on Market research and a 3% market growth several scenarios can be generated in Therapy Cost to determine the impact of inclusion of Spiriva in the market. These data are also shown in the MKT of the excel spreadsheet.

Figure 8. Market Share and Population Distributions.

MarketShare

	Yr 1	Yr 2	Yr 3
Ipratropium	55	53	53
Salmeterol	10	8	5
Advair	35	39	42
Spiriva	20	29	40
Ipratropium	39	34	26
Salmeterol	8	6	4
Advair	33	31	30

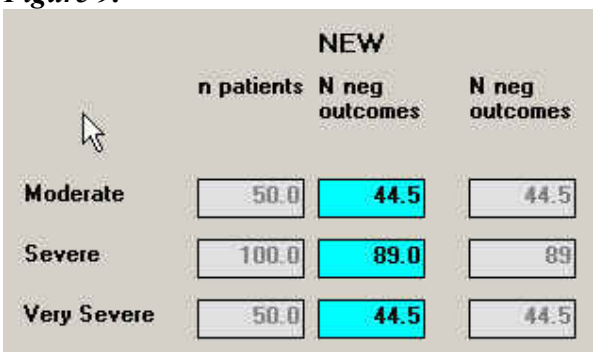
Population Growth 3%

Moderate Disease	258	265	273
Severe Disease	515	530	546
Very Severe disease	258	265	273
	1030	1061	1093

G. Exacerbations Avoided

The exacerbation data is entered in the Therapy Cost model after running the Budget Impact Analysis. In the case of SPIRIVA, clinical trail data shows 0.89 exacerbations per person per year. This information is entered in Therapy Cost as shown in the Figure below. Similarly the exacerbations for other drugs are also entered in the model.

Figure 9:

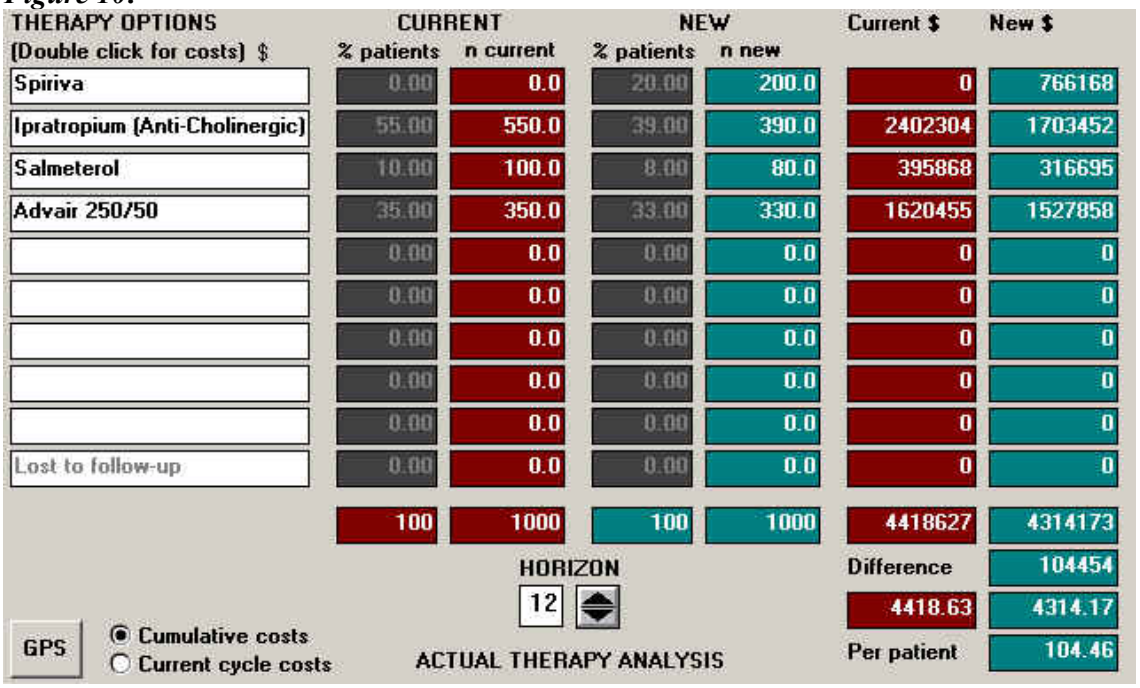


This concludes the specification of the Therapy Cost model and now the model can be run to get the results.

5. Results

Therapy Cost model was developed to conduct Budget Impact and the Cost Effectiveness Analysis. After the complete model has been specified and checked for accuracy in specification, you can now run the model either by clicking on the Budget Impact or the Cost Effectiveness Buttons. The results from the Budget Impact are shown in Figure 10.

Figure 10:



The results for per patient cost from the CE model are shown below in Figure 11 and the Incremental CE ratio between SPIRIVA and Advair are shown below in Figure 12.

Figure 11: Results of the Per Patient Cost

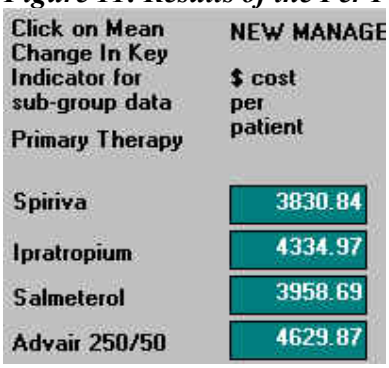
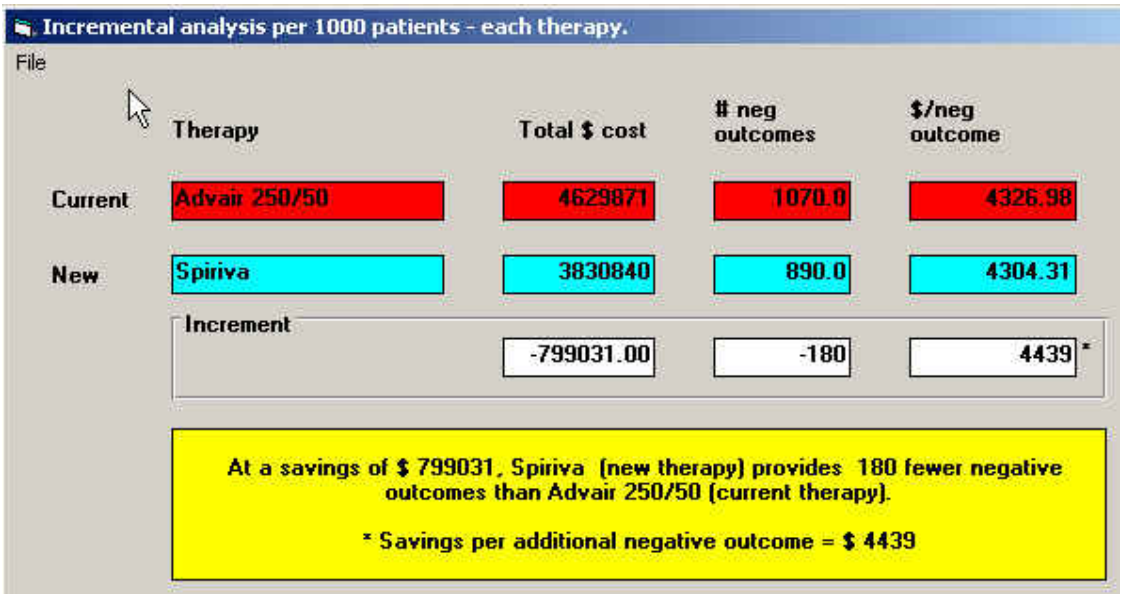


Figure 12: Incremental CE between SPIRIVA and Advair



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